

Drug Class Review on Pharmacologic Treatments for ADHD

Final Report Update 1

May 2006



The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Marian S. McDonagh, PharmD
Kim Peterson, MS

Oregon Evidence-based Practice Center
Oregon Health & Science University
Mark Helfand, MD, MPH, Director

Copyright © 2006 by Oregon Health & Science University
Portland, Oregon 97201. All rights reserved.

OHSU

TABLE OF CONTENTS

INTRODUCTION	4
SCOPE AND KEY QUESTIONS	5
METHODS.....	7
LITERATURE SEARCH	7
STUDY SELECTION.....	8
DATA ABSTRACTION	8
QUALITY ASSESSMENT	8
EVIDENCE SYNTHESIS	9
RESULTS.....	10
OVERVIEW	10
OVERALL SUMMARY	12
<i>General</i>	12
<i>Young Children (Preschool Age; 3-5 years)</i>	13
<i>Children (Elementary School Age; 6-12 years)</i>	13
<i>Adolescents</i>	15
<i>Adults</i>	16
<i>Subgroups</i>	16
KEY QUESTION 1: EFFICACY	18
<i>Young Children (Preschool Age; 3-5 years)</i>	18
<i>Children (Elementary School Age; 6-12 years)</i>	18
Generalizability Issues	18
Stimulants	19
Comparison of Immediate Release and Sustained Release Formulations	19
Comparisons of SR Formulations	21
Immediate Release Formulations	22
Atomoxetine.....	27
<i>Adolescents (ages 13 to 17)</i>	29
<i>Adults</i>	30
KEY QUESTION 2: SAFETY	35
<i>Short-Term Trial Evidence in Young Children (Preschool Age; 3-5 years)</i>	35
<i>Short-Term Trial Evidence in Children (Elementary School Age: 6-12 years)</i>	35
Stimulants	35
Growth Effects	37
<i>Adolescents</i>	37
<i>Adults</i>	37
KEY QUESTION 3: SUBGROUPS	47
<i>Race or Ethnicity</i>	47
<i>Gender</i>	48
ADHD Subtypes	48
<i>Co-morbidity</i>	48
<i>Tic disorders including Tourette's Disorder</i>	49
<i>Mental Retardation</i>	49
<i>Autism</i>	51
<i>Epilepsy</i>	52
<i>Substance Abuse Disorders</i>	52
Oppositional Defiant Disorder	52
Bipolar Disorder	52
LIMITATIONS OF THIS REVIEW	53
OVERALL SUMMARY	54
REFERENCES	59

IN-TEXT TABLES

Table 1. ADHD drugs and doses	6
Table 2. Numbers of Head to Head Trials of Drugs for ADHD	11
Table 3. Effect sizes for MPH CD and MPH OROS by time of day (COMACS study)	21
Table 4. Dextroamphetamine IR versus Methylphenidate IR Study Characteristics	22
Table 5. Comparison of Response Rates to MPH IR.....	23
Table 6. Maintenance of MPH IR short-term effects.....	26
Table 7. Adult ADHD - Response Rates from Placebo-Controlled Trials.....	32
Table 8. Adult ADHD – Other symptom-related outcomes in PCTs.....	32
Table 9. Long-term functional outcomes of MPH from Hechtman 1984	33
Table 10. Summary of Adverse Effects Reported	36
Table 11. Specific Adverse Events in placebo-controlled trials of adults.....	38
Table 12. Long-Term Height and Weight Outcomes in Observational Studies.....	40
Table 13. Tic-related outcomes in observational studies	43
Table 14. Cardiovascular risk of ADHD drugs	44
Table 15. Tic Severity Ratings in trials of drugs to treat ADHD	49
Table 16. Main Outcomes in Studies in Children with ADHD and Mental Retardation	50
Table 17. Adverse Events in Studies in Children with ADHD and Mental Retardation.....	51
Table 18. Overall Table Summary	54

FIGURES

Figure 1. Pharmacologic Treatments in ADHD: Drug Class Review Flow Diagram.....	70
---	----

APPENDICES

Appendix A. Scales Used to Assess Efficacy and Adverse Events.....	71
Appendix B. Search Strategies.....	78
Appendix C. Quality assessment methods for drug class reviews for the Drug Effectiveness Review Project.....	83
Appendix D. Study citations identified through public comment process	87
Appendix E. Excluded Studies.....	89
Appendix F. Previous systematic reviews.....	111

Evidence Tables – published in a separate document.*Suggested Citation:*

McDonagh MS, Peterson K. Drug Class Review on Pharmacologic Treatment for ADHD. Final Report. <http://www.ohsu.edu/drugeffectiveness/>

Funding:

The funding source, the Center for Evidence-based Policy, is supported by 17 organizations, including 15 state Medicaid programs. These organizations selected the topic and had input into the Key Questions for this review. The content and conclusions of the review are entirely determined by the Evidence-based Practice Center researchers. The authors of this report have no financial interest in any company that makes or distributes the products reviewed in this report.

Highlighting indicates evidence new for Update 1.

INTRODUCTION

According to the most recent NIH Consensus Statement (1998), “attention deficit hyperactivity disorder (ADHD) is the most commonly diagnosed childhood behavioral disorder.”¹ Classification of hyperactivity and defects in attention emerged in the 1960’s as Minimal Brain Dysfunction (MBD) and Hyperkinetic Syndrome, and has continued to evolve over time.²

A number of community-based studies have reported ADHD prevalence rates that range from 1.7% to 16%.³ This is broader than the range of 3 to 5 percent that was estimated by the expert panelists that participated in the NIH Consensus Development Conference on Diagnosis and Treatment of Attention Deficit Hyperactivity Disorder (ADHD) in 1998.¹ The estimated prevalence cited in the most recent (1997) version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) is 3 to 7 percent.⁴ Differences in prevalence estimates may be due to variation in methods of ascertainment and diagnostic criteria.⁵ While no independent diagnostic test exists for ADHD, the DSM-IV provides standardized criteria that can be used as a foundation for clinical diagnosis.^{1,4} According to the DSM-IV, essential features of ADHD include persistent levels of inattention, impulsivity and/or hyperactivity that exceed usual developmental patterns.⁴ In order to qualify for a DSM-IV diagnosis of ADHD, symptoms must date back to before age 7, persist for at least six months, and cause impairment that interferes with functional capacity in at least two performance settings (social, academic, or employment).⁴ DSM-IV specifies three distinct subtypes of ADHD that are characterized by predominantly inattentive, hyperactive-impulsive, or mixed symptoms.⁴

ADHD is diagnosed more frequently in males than in females.⁶ Comorbidities such as mood, anxiety and/or conduct disorders, tics or Tourette syndrome, learning disorders and mental retardation may be found in up to 65% of individuals with ADHD.³ With regard to the course of ADHD, symptoms can persist into adolescence in 80 percent of cases and into adulthood in 65 percent of cases.⁶ Comorbid DSM-IV mood, anxiety, substance use, and/or impulse disorders also commonly occur in combination with ADHD in adults.⁷

Historically, drug therapy of ADHD has consisted primarily of stimulant medications. More recently, nonstimulant medication treatment alternatives have been identified and these include atomoxetine, atypical antipsychotics, bupropion, clonidine, and guanfacine. Nonstimulant treatment options *may* offer advantages for individuals (1) seeking medications that have not been identified as having potential for abuse; (2) with concern over the *potential* long-term effects of stimulants on growing children; (3) with a history of nonresponse to or poor tolerance of stimulants; and/or (4) in whom stimulants are contraindicated due to co-existing medical and/or behavioral disorders and/or concomitant medications. Atomoxetine is the only nonstimulant evaluated in this review.

The actions of each of the medications included in this review are briefly described below. Throughout the report dextroamphetamine will be abbreviated to DEX and methylphenidate will be abbreviated to MPH.

Amphetamine mixture (Amphetamine mixture): Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. **Dextroamphetamine sulfate** is the dextro isomer of the compound *d,l* -amphetamine sulfate, a sympathomimetic amine of the amphetamine group.

Atomoxetine HCl : The precise mechanism by which atomoxetine produces its therapeutic effects in ADHD is unknown, but is thought to be related to selective inhibition of the pre-synaptic norepinephrine transporter, as determined in ex vivo uptake and neurotransmitter depletion studies.

Methylphenidate HCl is a mild central nervous system stimulant. The mode of action in man is not completely understood, but it presumably activates the brain stem arousal system and cortex to produce its stimulant effect. **Dexmethylphenidate HCl** is the more pharmacologically active enantiomer of the *d* - and *l* –enantiomers of methylphenidate, is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

Modafinil: Modafinil is a central nervous system stimulant approved for promoting wakefulness, although the precise mechanism(s) is unknown. Modafinil has wake-promoting actions like sympathomimetic agents including amphetamine and methylphenidate, although the pharmacologic profile is not identical to that of sympathomimetic amines. At pharmacologically relevant concentrations, modafinil does not bind to most potentially relevant receptors for sleep/wake regulation, including those for norepinephrine, serotonin, dopamine, GABA, adenosine, histamine-3, melatonin, or benzodiazepines. Modafinil also does not inhibit the activities of MAO-B or phosphodiesterases II-V. While only FDA-approved for narcolepsy treatment, modafinil is also being used to treat ADHD.

Scope and Key Questions

The purpose of this review is to compare the benefits and harms of different pharmacologic treatments for ADHD. The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

Key Question 1. What is the comparative effectiveness of different pharmacologic treatments for attention deficit disorders?

Key Question 2. What is the comparative tolerability and safety of different pharmacologic treatments for attention deficit disorders?

Key Question 3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications, or co-morbidities for which one pharmacologic treatment is more effective or associated with fewer adverse events?

Inclusion Criteria

Populations

Pediatric and adult outpatients with Attention Deficit Disorders

- Attention Deficit Disorder
- Attention Deficit Hyperactivity Disorder

Interventions (immediate release and extended release formulations, where applicable)

Table 1. ADHD drugs and doses

Generic Name	Trade Name*	FDA ADHD Approval	Year Introduced
Amphetamine mixture**	Adderall®*	Children	1960
	Adderall XR®***	Both	2001
Atomoxetine HCl	Strattera®	Both	2002
Dextroamphetamine sulfate	Dexedrine®*	Children	1976
	Dextrostat®*	Children	1975
	Dexedrine Spansule®	Children	Unknown
Dexmethylphenidate HCl	Focalin®*	Children	2001
Methylphenidate HCl	Concerta® (MPH OROS)	Children	2000
	Metadate CD® (MPH CD)	Children	2001
	Metadate ER® (MPH ER)	Both	1999
	Methylin®	Both	2003
	Ritalin®*	Both	1955
	Ritalin SR® (MPH SR)	Both	1982
	Ritalin LA® (MPH SODAS)	Children	2002
Modafinil	Provigil®	Adults	1998

*or generic equivalent

** (amphetamine aspartate; amphetamine sulfate; dextroamphetamine saccharate; dextroamphetamine sulfate)

***Notice of Compliance (NOC) suspended in February 2005 by Health Canada in response to case reports of sudden/cardiac death and/or stroke. NOC was reinstated in August 2005 and is again available for prescription in Canada

Outcomes

- Symptom response (inattention, hyperactivity-impulsivity, aggression, global ratings, etc.)
- Functional capacity (social, academic and occupational productivity)
- Caregiver satisfaction (parent, teacher)
- Quality of life (child, parent, caregivers, teachers)
- Overall adverse effect reports
- Withdrawals due to adverse effects
- Serious adverse events reported
- Specific adverse events (hepatotoxicity, insomnia, anorexia, effects on growth, abuse potential)
- Time to onset of effectiveness
- Duration of effectiveness

Scales and Tests Used to Measure Outcomes

Numerous ADHD-specific and other psychiatric rating scales, as well as neuropsychological testing methods, are used to measure symptoms of ADHD. We limited our analyses to rating scales/tests for which we found published evidence of good reliability and validity. Our primary sources for documentation of the psychometric properties of rating scales included the Agency for Healthcare Research and Quality (AHRQ) Technical Review #3 (Diagnosis of Attention-Deficit/Hyperactivity Disorder)⁸ and Mental Measurements Yearbooks.⁹⁻¹⁶ The AHRQ Technical Review #3 provides qualitative information on many of the rating scales cited in our report, including “subscales included in each test, comorbid conditions addressed by each checklist, time required to administer, number of items, ages for which norms are available, computer scoring availability, and ordering information, including cost” and reliability and validity. Appendix A provides a listing of commonly used scales and tests and associated acronyms.

Study Designs

- Controlled clinical trials and good-quality systematic reviews
- Observational studies with functional or adverse event outcomes

The benefit of the RCT design is the ability to a reliably unbiased estimate of treatment effects in a controlled setting, by randomizing patients is the best method of producing comparable groups based on both known and unknown prognostic factors.^{17,18} However, RCTs can vary in quality, and often suffer from limitations in generalizability to the larger patient population. Observational study designs are thought to have greater risk of introducing bias, although they typically represent effects in a broader section of the overall patient population. While it has been shown that some observational studies and RCTs of the same treatments have similar findings, there are also multiple example of situations where this has not been true and the question of what type of evidence is best has not been resolved.^{19,20} While RCTs also provide good evidence on short-term adverse events, observational designs are useful in identifying rare, serious adverse events which often require large numbers of patients exposed to a treatment over longer periods of time to be identified.

METHODS

Literature Search

To identify relevant citations, we searched the Cochrane Central Register of Controlled Trials (4th Quarter 2005), Cochrane Database of Systematic Reviews, MEDLINE (1966 to October Week 1 2005), EMBASE (2nd Quarter 2004), and PsycINFO (1974 to September Week 4 2005) using terms for included drugs, indications, and study designs (see Appendix B for complete search strategies). We have attempted to identify additional studies through searches of reference lists of included studies and reviews, the FDA web site, as well as searching dossiers submitted by pharmaceutical companies for the current review. All citations were imported into an electronic database (EndNote 9.0).

Study Selection

We assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above. Full-text articles of potentially relevant abstracts were retrieved and a second review for inclusion was conducted by reapplying the inclusion criteria.

Data Abstraction

The following data were abstracted from included trials: study design, setting, population characteristics (including sex, age, *ethnicity*, diagnosis), eligibility and exclusion criteria, interventions (dose and duration), comparisons, numbers screened, eligible, enrolled, and lost to follow-up, method of outcome ascertainment, and results for each outcome. We recorded intention-to-treat results when reported. If true intention-to-treat results were not reported, but loss to follow-up was very small, we considered these results to be intention-to-treat results. In cases where only per-protocol results were reported, we calculated intention-to-treat results if the data for these calculations were available. In trials with crossover, outcomes for the first intervention were recorded if available. This was because of the potential for differential withdrawal prior to crossover biasing subsequent results and the possibility of either a “carryover effect” (from the first treatment) in studies without a washout period, or “rebound” effect from withdrawal of the first intervention.

Data abstracted from observational studies included design, eligibility criteria duration, interventions, concomitant medication, assessment techniques, age, gender, ethnicity, number of patients screened, eligible, enrolled, withdrawn, or lost to follow-up, number analyzed, and results.

Quality Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria listed in Appendix C. These criteria are based on the U.S. Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (U.K.) criteria.^{21, 22} We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intention-to-treat analysis. Trials that had a fatal flaw in one or more categories were rated “poor-quality”; trials that met all criteria were rated “good-quality”; the remainder were rated “fair-quality.” A fatal flaw occurs when there is evidence of bias or confounding in the trial, for example when randomization and concealment of allocation of random order are not reported and baseline characteristics differ significantly between the groups. In this case, randomization has apparently failed and for one reason or another bias has been introduced.

As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair-quality studies are *likely* to be valid, while others are only *probably* valid. A poor-quality trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs. External validity of trials was assessed based on whether the publication adequately described the study population, how similar patients were to the target population in whom the intervention will be applied, and whether the treatment received by the control group was reasonably representative of standard practice. We also recorded the role of the funding source.

Appendix C also shows the criteria we used to rate observational studies. These criteria reflect aspects of the study design that are particularly important for assessing adverse event rates. We rated observational studies as good-quality for adverse event assessment if they adequately met six or more of the seven predefined criteria, fair-quality if they met three to five criteria and poor-quality if they met two or fewer criteria.

Included systematic reviews were also rated for quality based on pre-defined criteria (see Appendix C), based on a clear statement of the questions(s), inclusion criteria, adequacy of search strategy, validity assessment and adequacy of detail provided for included studies, and appropriateness of the methods of synthesis.

Overall quality ratings for the individual study were based on internal and external validity ratings for that trial. A particular randomized trial might receive two different ratings: one for effectiveness and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the set of studies relevant to the question.

Evidence Synthesis

Effectiveness versus Efficacy

Throughout this report, we highlight *effectiveness* studies conducted in primary care or office-based settings that use less stringent eligibility criteria, assess health outcomes, and have longer follow-up periods than most *efficacy* studies. *Effectiveness* studies conducted in primary care or office-based settings use less stringent eligibility criteria, assess health outcomes, and have longer follow-up periods than most efficacy studies. The results of effectiveness studies are more applicable to the “average” patient than results from highly selected populations in efficacy studies. Examples of “effectiveness” outcomes include quality of life, global measures of academic success, and the ability to work or function in social activities. These outcomes are more important to patients, family and care providers than surrogate or intermediate measures such as scores based on psychometric scales.

An evidence report pays particular attention to the generalizability of *efficacy* studies performed in controlled or academic settings. *Efficacy* studies provide the best information about how a drug performs in a controlled setting that allow for better control over potential confounding factors and bias. However, the results of efficacy studies are not always applicable to many, or to most, patients seen in everyday practice. This is because most efficacy studies use strict eligibility criteria which may exclude patients based on their age, sex, medication compliance, or severity of illness. For many drug classes severely impaired patients are often excluded from trials. Often, efficacy studies also exclude patients who have “comorbid” diseases, meaning diseases other than the one under study. Efficacy studies may also use dosing regimens and follow up protocols that may be impractical in other practice settings. They often restrict options, such as combining therapies or switching drugs that are of value in actual practice. They often examine the short-term effects of drugs that, in practice, are used for much longer periods of time. Finally, they tend to use objective measures of effect that do not capture all of the benefits and harms of a drug or do not reflect the outcomes that are most important to patients and their families.

Data Presentation

We constructed evidence tables showing the study characteristics, quality ratings, and results for all included studies. Studies that evaluated one pharmacologic treatment of ADHD against another provided direct evidence of comparative benefits and harms. Outcomes of changes in symptom measured using scales or tools with good validity and reliability are preferred over scales or tools with low validity/reliability or no reports of validity/reliability testing. Where possible, head-to-head data are the primary focus of the synthesis.

In theory, trials that compare these drugs to other interventions or placebos can also provide evidence about effectiveness. This is known as an indirect comparison and can be difficult to interpret for a number of reasons, primarily issues of heterogeneity between trial populations, interventions, and assessment of outcomes. Indirect data are used to support direct comparisons, where they exist, and are also used as the primary comparison where no direct comparisons exist. Such indirect comparisons should be interpreted with caution.

Throughout the report dextroamphetamine will be abbreviated to DEX and methylphenidate will be abbreviated to MPH.

RESULTS

Overview

We identified a total of 2,433 citations from literature searches, reviews of reference lists, pharmaceutical manufacturer dossier submissions, and public comment. Of these, 152 were identified in the most recent update. Dossiers were submitted by six pharmaceutical manufacturers for the original review: Shire US (amphetamine mixture, Amphetamine mixture XL), Eli Lilly (atomoxetine HCl), McNeil (methylphenidate HCl, Concerta®), Novartis (methylphenidate HCl, Ritalin LA®), and Cephalon (modafinil). Shire US (amphetamine mixture, amphetamine mixture XL), Eli Lilly (atomoxetine HCl), and McNeil (methylphenidate HCl, Concerta®) submitted additional dossiers for this most recent update. After applying the eligibility and exclusion criteria to the titles and abstracts, we obtained full-paper copies of 583 publications. After re-applying the criteria for inclusion, we ultimately included 196 publications (144 studies and 43 duplicate data or background publications). Appendix D lists studies pending review that were identified in the course of the public comment process for this most recent update. A list of excluded studies is reported in Appendix E. The flow of study inclusion and exclusion is detailed in Figure 1.

We identified the following numbers of head to head comparative trials of pharmacologic treatments for ADHD.

Table 2. Numbers of Head to Head Trials of Drugs for ADHD

	MPH IR	MPH ER	DEX	DEX-MPH	Adderall	Modafinil	Atomoxetine
MPH IR							
MPH ER	C: 8 T: 1	C: 2					
DEX	C: 11 A: 1						
DEX-MPH	--	--	--				
Adderall	C: 5		C: 1	--			
Modafinil	--	--	A: 1	--	--		
Atomoxetine	C: 3	C: 1	--	--	C: 1	--	

C= children
T= adolescents
A= adults

Data abstracted from these trials can be found in Evidence Table 3 and 9 and the relevant quality assessments in Evidence Table 4 and 10. We found hundreds of placebo-controlled trials in children. The majority were studies of MPH IR and fewer of various other formulations (OROS, SR and MR). Placebo-controlled trials also studied DEX, Adderall, unspecified “psychostimulants”, atomoxetine, and modafinil, and “amphetamine”. Because there are a large number of head to head trials, and indirect comparisons from placebo controlled trials are less reliable, we have only included placebo-controlled trials of drugs for which we have limited or no head to head evidence (atomoxetine, dexamethylphenidate, MPH ER, MPH CD or modafinil). Also for Key Question 1, we included 6 placebo-controlled and 3 multimodal trials and 5 observational studies as the only evidence of remission rates and long-term functional outcomes and response maintenance. One trial of the effects on weight and height of children discontinuing MPH during summers was included (MPH versus no treatment) was included in Key Question 2. We also included 19 placebo-controlled trials in subgroup populations in Key Question 3. Data abstracted from placebo controlled trials can be found in Evidence Table 5, and relevant quality assessments in Evidence Table 6. For long-term safety, we included 19 observational studies (Evidence Tables 15 and 16).

In adult populations (age 18 and above), we included 20 placebo-controlled trials (Evidence Tables 11 and 12), and one long-term observational study (Evidence Tables 15 and 16) in addition to the head to head trials listed in Table 2 above.

Previous Systematic Review Findings

Three good quality systematic reviews of drug treatments for ADHD were conducted prior to this review, one in the US⁵, one in Canada⁵, and one in the UK²³, were included. There are some differences in the lists of drugs reviewed amongst these reviews and our report, with the commonalities being MPH IR and SR formulations, DEX, atomoxetine, bupropion, and clonidine. The Canadian and British reviews did not include adults. These reviews consistently found a lack of evidence of a difference between the drugs studied in efficacy or adverse events. In some part, the reason for not finding a difference was thought to be due to small sample sizes lacking power to find a difference, and some studies were given less weight due to poor quality. Differences in adverse events were thought to be minor, although the assessment and reporting of adverse events was criticized. These reviewers also commented on the lack of good quality studies assessing long-term outcomes, both of effectiveness and serious adverse events. See Appendix F for further description of the findings of these reviews.

The American Academy of Pediatrics Clinical Practice Guideline on treatment of school-aged children with ADHD was also reviewed.²⁴ The guideline considers only stimulant medications, specifically all forms of MPH and DEX. Stimulant and/or behavior therapy is recommended, the guideline does not prefer one, and states that the Jadad review (cited above) found no difference between these stimulants. The guideline also states, “Individual children, however, may respond to one of the stimulants but not to another.”

What This Review Adds

Our review adds to these prior reviews in a number of areas. Cross-referencing lists of studies included in each review reveals that we have included several studies that the other reviews did not.²⁵⁻⁴⁸ Some of the reasons for these studies not being included in the other reviews are differences in the scope of drugs reviewed, the outcomes included, and study designs included. For example, our review included Adderall and modafinil, which were not included in these reviews. Importantly, the current review includes observational studies to assess harms and functional outcomes and RCTs with functional outcomes such as academic achievement that were not included in these previous reviews. This review includes comparative evidence on the effect of MPH on weight and height, which was not included in the previous reviews. In addition, special effort has been made to identify the effects of ADHD subtype, diagnostic tool or definition, primary outcomes, comorbidities and ethnicity.

Overall Summary of the Evidence on Efficacy or Effectiveness, Short-Term Efficacy and Tolerability, and Long-Term Safety of Drugs Used to Treat ADHD

General

- There are no *trials* of comparative effectiveness of these drugs for treatment of ADHD.
- Good quality evidence on the use of drugs to affect outcomes relating to global academic performance, consequences of risky behaviors, social achievements, etc. is lacking.
- The evidence for comparative efficacy and adverse events of drugs for treating ADHD is severely limited by small sample sizes, very short durations, and the lack of studies measuring functional or long-term outcomes. Methods of measuring symptom control vary significantly across studies. The crossover design was frequently used, with few analyzing the effect of order of administration of drugs and those that did found a significant effect. No head-to-head efficacy trial was good quality. The small numbers of patients in these trials limits the ability to show a difference between drugs if one exists.
- Limitations to the generalizability of these trials include the following.
 - Characterization of ADHD symptomatology across studies is limited due to use of varied or indeterminate diagnostic processes.
 - Minorities and the most seriously ill patients were underrepresented.
 - The small sample sizes of these trials did not allow for statistical analyses of potential effects of these factors.
- Overall, the rate of response to stimulants appears to be in the range of 60 to 80%; however the definitions of response rate varied and may not be comparable. Depending on the definition used, there is lack of clarity on the relationship of response rate to clinical significance. Response rates of nonstimulants vary, but the range in placebo-controlled trials is similar to that found with stimulants. Significant variation in the

method of assessment and definition of response are most likely the reason for the wide variation.

Young Children (Preschool Age; 3-5 years)

Efficacy and tolerability

- No comparative evidence in young children was found.
- MPH was superior to placebo in efficacy in only 1 of 3 fair-quality placebo-controlled trials that used a validated assessment tool (CPRS-R); but was also associated with higher rates of adverse events.

Long-Term Safety

- We found no evidence on long-term safety of drugs used to treat ADHD in young children.

Children (Elementary School Age; 6-12 years)

Effectiveness

- Because no trials of effectiveness were found, observational studies were assessed for outcomes of effectiveness.
- The only comparative study with relevant outcomes found MPH OROS to be associated with fewer outpatient visits/hospitalization for accidents/injury than MPH IR over 12-months. Methodologic concerns over this study suggest caution in interpretation of these findings.
- Uncontrolled observational data assessing the effect of duration of treatment with MPH IR found no differences in academic achievement as measured by teachers, the proportion repeating grades, in special education classes or being tutored. Again, significant methodologic limitations suggest caution in interpreting these findings.

Efficacy and tolerability

Stimulants

- Immediate Release versus Extended Release formulations
 - Including the largest RCT, with 312 children, 2 studies of MPH IR versus MPH OROS (Concerta®) and 1 study of MPH IR versus MPH ER (Medkinet®) did not show an overall difference in outcomes. Very limited evidence was mixed in the comparison on MPH IR and MPH SR (Ritalin SR®).
 - Database studies using intermediate outcomes report greater persistence with MPH OROS and MPH SODAS compared to MPH IR. Methodologic concerns indicate caution in interpreting this evidence.
- Sustained Release versus Sustained Release
 - Very limited evidence suggests that MPH XR (Ritalin LA®) was superior to MPH OROS (Concerta®) on some, but not all efficacy outcomes. However, these results should be interpreted with caution until further evidence is available. We did not find evidence of a difference in adverse events between IR and SR formulations.

- The COMACS study results suggest that MPH CD was associated with significantly larger effect sizes than MPH OROS in the morning, treatment effects were similar in the afternoon, and MPH OROS was superior in the evening. Methodologic concerns indicate caution in interpreting these findings.
- Dextroamphetamine versus Methylphenidate
 - The body of evidence clearly indicates no difference in efficacy between DEX and MPH IR. Evidence from short-term trials and observational studies suggests that weight loss is greater with DEX than MPH IR.
- Adderall® versus Methylphenidate
 - Amphetamine mixture was superior to MPH IR on a few efficacy outcome measures in two trials, but clear evidence of superiority is lacking. Very limited evidence suggests that twice daily dosing of Amphetamine mixture led to higher rates of loss of appetite and sleep trouble than once daily dosing or MPH IR.
- Dextroamphetamine versus Adderall®
 - Evidence on the comparison of DEX IR versus SR versus Amphetamine mixture is limited and conflicting, but may suggest that measures made in the morning show DEX IR superior to DEX SR, and afternoon measures show DEX SR superior to Amphetamine mixture. Transient weight loss was greater with Amphetamine mixture and DEX SR than with DEX IR. However, this evidence should be interpreted with caution.
- Longer-term trials of MPH IR, placebo or non-medication treatments provide some evidence to assess the ability of MPH IR to maintain effects longer periods of time. These trials report somewhat mixed results on the ability to maintain short-term improvements in symptoms over 6 to 24 months. While the 14-month MTA found no deterioration over time, 3 other studies found the reverse. One explanation for this finding may be dose. One study found that the higher dose groups did not have deterioration of the gains in symptom control of inattentiveness and hyperactivity, and found an overall dose-response. The mean dose in the MTA study was also higher than in these other trials, and used 3 doses per day. A 10-month follow up of patients from the MTA study showed a decrease in the magnitude of effect.

Atomoxetine

- Atomoxetine
 - Limited evidence suggests that atomoxetine was associated with efficacy outcomes similar to MPH IR in one trial, but was associated with less significant efficacy outcomes than the extended release (XR) form of amphetamine mixture in another trial.
 - Atomoxetine was associated with significantly higher rates of vomiting and somnolence than both MPH IR and amphetamine mixture XR, while MPH IR caused more 'abnormal thinking' and amphetamine mixture XR caused more insomnia.

Long-Term Safety

- Although the observational studies provide some estimate of the prevalence of serious longer-term adverse events with amphetamine mixture, atomoxetine, DEX, and MPH (IR

and SR), few studies directly compared different pharmacologic treatments for ADHD for any one adverse event.

- For outcomes where only uncontrolled evidence is available, it is not possible to draw conclusions about comparative long-term safety through indirect comparisons across observational studies due to large differences in study characteristics.
- The overall body of evidence is poor quality due to a variety of flaws in design and analysis and should be interpreted with caution.
- Height Change in Children
 - Evidence on DEX vs MPH or MPH IR alone is inconsistent. No conclusions can be drawn.
 - Limited evidence suggests that height changes resulting from atomoxetine are similar to those reported with MPH IR, and are also transient.
- Weight in children
 - DEX vs MPH: Results from comparative observational studies suggest that DEX is associated with significantly greater suppression of weight gain than MPH in the first 1-2 years. However, the difference between DEX and MPH appears to resolve by the second year and the difference found in years 1-2 may have been exaggerated by higher relative DEX dosages. Ultimately, these data should be interpreted with caution, due to methodological flaws in the measurement of weight.
 - The remaining comparative and noncomparative observational studies do not support a definite relationship between MPH and suppression of weight gain.
 - Limited evidence suggests that weight changes resulting from atomoxetine are similar to those reported with MPH IR, and are also transient.
- There is no comparative evidence on other long-term safety outcomes, including tics, seizures, cardiovascular adverse events, injury frequency, and hepatotoxicity.
- Post-marketing safety concerns: Labeling revisions, changes in market availability:
 - Adderall XR® Canadian licensure reinstated in August 2005, following temporary suspension by Health Canada in February 2005 due to reports of sudden death in children.
 - Atomoxetine: reports of severe hepatotoxicity and risk of suicidality led to additional warnings in product label.

Adolescents

Efficacy and tolerability

- Adolescents were studied in a small number of short-term trials that involved MPH IR or MPH OROS (Concerta®). Studies of atomoxetine included adolescents and are discussed above.
- MPH OROS vs MPH IR
 - A single, very small, *single blinded*, study showed MPH OROS superior to MPH IR on some measures of simulated driving skills, during tests administered in the late evening or nighttime. No difference was found during other test times.
- Indirect Evidence: Stimulants
 - Placebo-controlled trials of MPH IR do not provide indirect evidence of comparative efficacy or tolerability due to heterogeneity in outcome reporting.

- MPH IR generally was superior to placebo in improving core ADHD symptoms, but was associated with more frequent reports of appetite and sleep disturbances.
- Functional outcomes: observational studies
 - Observational studies of MPH IR that report functional outcomes found mixed results. In an uncontrolled study of young adult males who had taken MPH as children (mean age at discontinuation of MPH 17 years) fewer suicide attempts were associated with higher dose of MPH. Emancipated living situation and level of relationship commitment was associated with response to MPH. Early response to MPH was negatively associated with high school graduation, however.
 - Another uncontrolled follow-up of MPH IR responders reported “improved grades” after 6 – 14 months. Methodological limitations of these studies severely limit the interpretation these findings.

Long-Term Safety

- We found no evidence on long-term safety of drugs used to treat ADHD in adolescents

Adults

Efficacy and tolerability

- Pharmacological treatment of ADHD in adults has not been widely studied.
- Adderall, DEX IR, and MPH IR lead to response in 57-70.4% of participants in placebo-controlled trials.
- There is no evidence that any one stimulant is more effective than any other.
- Other pharmacologic treatments have emerged that offer viable alternatives to traditional stimulant therapy and response rates are as follows:
 - Atomoxetine: 52.4%
 - Modafinil: 48%
- Evidence regarding treatment effects on quality of life and other ADHD-related symptoms (depressed mood, anxiety, and cognition) in adults is not compelling.
- Short-term, randomized controlled trials do not provide clear evidence that any one stimulant is more tolerable than another or that nonstimulants offer an advantageous tolerability profile over stimulants.
- No conclusions about comparative efficacy or safety in subgroups of adults can be made.

Long-term safety

- We found one follow-up study of participants in an MPH IR RCT that reported a single attempted suicide among 8 men (12.5%).

Subgroups

- Race / Ethnicity
 - Only ½ of studies reported race or ethnicity data; Studies were primarily conducted in white populations
 - 2 placebo-controlled studies in 100% non-White groups:
 - MPH IR in African American boys
 - 75% of subscale measures showed improvement

- This rate is similar to response rates reported in other trials
 - Linear increases in diastolic blood pressure noted
 - Improvements compared to baseline on 90% of measures
- Gender
 - No difference in efficacy can be found between boys and girls.
- Commonly occurring comorbidities:
 - ½ of studies reported, but none stratified analyses
 - Prevalence in studies (AAP estimated prevalence)
 - oppositional defiant disorder: 19-66.7% (35.2)
 - conduct disorder 9-38.5% (25.7)
 - anxiety 1.4-42% (25.8)
 - depression 0.7-6.6% (18.2)
 - Adults: Atomoxetine: Subgroup analyses of placebo-controlled trials suggested that presence or absence of co-occurring “Psychiatric illness” did not alter treatment effects
- Tics
 - Placebo-controlled studies of MPH IR do not consistently support a relationship to increased tic severity or frequency. A few measures improved or worsened, but global measures and total scores do not show a difference.
- Mental Retardation / Developmental Delay
 - In children with mental retardation, evidence indicates that MPH IR is beneficial on most ADHD outcomes compared to placebo.
 - Adverse events were common, with staring and social withdrawal occurring more often with MPH IR than placebo.
- Autism or Epilepsy
 - Very limited evidence is available on the use of MPH IR in children with autism or epilepsy. However, this evidence suggests that MPH IR is beneficial on most ADHD outcomes compared to placebo. This evidence should be interpreted with caution.
- Oppositional Defiant Disorder
 - Very limited evidence indicates that atomoxetine was associated with significantly greater improvements in ADHD outcomes than placebo
- Bipolar Disorder
 - Very limited evidence indicates that mixed amphetamine salts (Adderall®) was associated with significantly greater improvements in ADHD outcomes than placebo when added to divalproex in children with co-existing bipolar disorder
- Substance Abuse
 - Very limited evidence suggests that response rates to MPH IR in Adults: with co-occurring cocaine dependence was similar to rates found in other trials.
- No conclusions about *comparative* effectiveness or safety based on age, gender, race/ethnicity or comorbidities can be made from this body of evidence.

Detailed Assessment

Key Question 1: Efficacy.

What is the comparative efficacy or effectiveness of different pharmacologic treatments for attention deficit disorders?

Young Children (Preschool Age; 3-5 years)

Evidence on the effectiveness of pharmacotherapy for ADHD in young children is seriously lacking (Evidence Tables 1 and 2). We did not find any effectiveness trials, long-term observational studies assessing functional outcomes or efficacy trials comparing drugs in young children with ADHD.

The evidence of any short-term benefit of stimulants in this age group comes from five placebo-controlled trials of MPH IR.⁴⁹⁻⁵⁴ However, only 1 trial was fair quality and used an assessment tool with good validity (CPRS-R; learning, conduct and hyperactivity indices only).⁵¹ In this study, both the high dose (0.5 mg/kg twice daily) and the low dose (0.3 mg/kg twice daily) resulted in lower scores than while on placebo at the end of 7 to 10 days of treatment. The high dose resulted in better final scores than the low dose on only the learning component of the CPRS-R with the low dose resulting in a mean of 8 points (10%) lower, and the high dose a mean of 14 points (18%) lower than the score while on placebo. The clinical importance of these differences is not known, and baseline scores are not reported or accounted for. Based on parental report, medication did not result in better compliance with tasks compared to placebo, although reports of time on task were better with the higher dose (mean 52 seconds longer compared to placebo). The DSM-III criteria were used to diagnose ADHD. ADHD subtypes or ethnicity were not identified in this study. MPH was associated with higher rates and greater severity of adverse events than placebo, significantly more in the higher dose group. Rates of specific adverse events were not reported. We found no evidence on long-term safety of drugs used to treat ADHD in young children.

Children (Elementary School Age; 6-12 years)

Generalizability Issues

Studies of elementary school age children with ADHD were characterized by under-reporting of baseline subtype classifications, race or ethnicity, co-occurring disorders, and illness severity. This gap in the literature limits the generalizability of the findings to target populations. Only one-quarter of all studies of school-aged children reported ADHD subtype prevalence rates. The mixed subtype was most common, occurring in 58-100% of participants across most study populations. The inattentive subtype was generally observed less frequently (prevalence rate range: 9-40%) and the hyperactive subtype was relatively rare (prevalence rate range: 1-8%). Only one-half of all studies of elementary school-aged children reported race or ethnicity among the baseline characteristics. The racial/ethnic make-up of the majority of these study populations was consistent with the current U.S. Census Bureau Estimates (white=80.4%, black=12.8%, Asian=4.2%, and of Hispanic/Latino origin=14.1%).⁵⁵ However, the prevalence of ADHD among ethnic groups may not correlate with these data.

Just over half of studies reported prevalence rates of co-occurring disorders, including oppositional defiant disorder (19-66.7%), conduct disorder (9-38.5%), anxiety (1.4-42%) and depression (0.7-6.6%). With the exception of depression, the ranges of comorbidities reported in these trials encompass the American Academy of Pediatrics estimates on prevalence of common

comorbidities: Oppositional defiant disorder=35.2 (27.2, 43.8), conduct disorder=25.7 (12.8, 41.3), anxiety disorder=25.8 (17.6, 35.3) and depressive disorder=11.1, 26.6).⁵⁶ Illness severity was not presented as a baseline characteristic in most studies, and comparisons across studies based on scales used to assess symptoms are hampered by variation in scale choice and method of reporting. Diagnostic processes also varied across studies. Seventy-two percent of studies used either the DSM III, DSM III-R, or DSM IV criteria to diagnose ADHD, however many used additional criteria and the clinical comparability of patients enrolled is not clear.

Stimulants

Methylphenidate

Comparison of Immediate Release and Sustained Release Formulations

We included eight trials of MPH IR versus SR formulations.^{26, 57-64} Of these, four were poor quality due to either inadequate or undescribed methods of randomization and allocation concealment, combined with lack of description of an intention to treat (ITT) analysis, lack of information on eligibility criteria, attrition, or post-randomization exclusions (Evidence Table 3).^{26, 57, 58, 63} The remaining 3 studies compared MPH OROS (Concerta®) or MPH SR (Ritalin SR®) to MPH IR.^{59, 61, 62} Also, according to an FDA statistical review (http://www.fda.gov/cder/foi/nda/2000/21-121_Concerta_statr.pdf), MPH OROS (Concerta®) and MPH IR were compared in an additional trial of 64 children that has not yet been published.⁶⁵

No trials comparing the other extended release formulations of MPH (Ritalin LA®, Methylin ER®, Metadate ER®, or Metadate CD®) to MPH IR were found.

MPH IR versus MPH OROS (Concerta®)

Two trials of MPH IR versus MPH OROS did not show overall differences in outcomes.⁵⁹⁻⁶¹ There were no significant differences between the formulations on the primary outcome measure (IOWA Conners scale) or on 11 secondary measures in an RCT of 312 children.⁶¹ While not reaching the level of ‘poor’ quality, some concerns about the study were identified. Although the randomization was stratified, the analyses were not and all data from patients enrolled at one study site were excluded from the analysis due to ‘irregularities in the data collection’. There were small differences between groups at baseline, including larger proportions of patients with comorbidities and a diagnosis of *inattentive* ADHD in the MPH IR group, and larger proportions of patients with a diagnosis of *combined* ADHD and who were taking MPH IR prior to enrollment in the MPH OROS group. The baseline inattention/overactivity score on the IOWA Conners parents scale was significantly higher in the MPH OROS group than the MPH IR group.

A much smaller crossover trial (70 children), 7 days long, found MPH OROS to have lower scores on the Abbreviated Conners Parents scale (total), and on the inattention/overactivity item (out of 16 items), however no differences were found based on assessments made by teachers and counselors.^{59, 60}

Findings from these 2 trials and a similar unpublished trial should be interpreted with caution, however, in light of some criticism from the FDA that the analysis methods used in all 3 were insufficient for evaluation of clinical equivalency (http://www.fda.gov/cder/foi/nda/2000/21-121_Concerta_statr.pdf).⁶⁵

MPH IR versus MPH SR (Ritalin SR®)

In a small 2-week RCT (34 children) of MPH IR versus MPH SR found mixed results.⁶² The outcome measures included questionnaires (not validated) completed by a physician, a teacher and a parent. The teacher questionnaires indicated significant differences in final total score and the “Conduct Problem” score favoring MPH IR. Parent questionnaires indicated a significant difference favoring MPH SR on the “Conduct Problem” item final score, and the physician scores showed no difference.

MPH IR vs MPH ER (Medikinet®)

Results from a fair-quality, 2.5-week crossover trial of 79 pediatric patients did not suggest any differences between flexible dosages (≤ 1 mg/kg) of MPH IR BID and MPH ER in SKAMP Attention or Deportment subscale scores or in math problems attempted.⁶⁴ Effect sizes were relatively similar regardless of time of day (9:30 am through 4:45 pm). Pediatric patients were mostly male (89.9%), with ADHD of the combined type (92.4%) and had a mean age of 10.0 years. This study was conducted in outpatient clinics in Germany and the formulation of MPH ER (Medikinet®) is not available in the U.S.

Other Measures of Comparative Effectiveness of IR vs SR formulations

Clinical trials of extended release versus immediate release formulations were too short to demonstrate differences in long-term health outcomes. However, the intermediate outcome measure of persistence (the proportion of patients continuing to take or refill prescriptions for a medication after some longer period of time) is thought to be a good proxy for extension of benefits seen in the short-term, or if none were found, evidence of a difference in longer-term, real-life settings. Persistence is an intermediate outcome with unknown validity because direct evidence of a relationship between persistence rates and long term health outcomes with ADHD drugs is lacking.

Two observational database studies reported persistence outcomes for 12-month periods following index prescriptions of MPH IR and ER formulations.^{41, 66} MPH ER formulations were associated with better persistence outcomes than MPH IR in both studies regardless of measurement methods. The findings of these studies should be interpreted with caution, however, until confirmed by a randomized controlled trial that would serve to rule out potential sources of bias, including between-group baseline differences in unmeasured clinical characteristics, physicians’ prescribing preferences, and differences in reasons for discontinuation (e.g., change in insurance benefit, use of promotional samples).

Data were derived from the Integrated Health Care Information Services (IHCIS) National Managed Care Benchmark Database in one study that reported the proportion of 1,775 patients that persisted with their index prescription for 12 months *with no discontinuations exceeding 14 days*.⁶⁶ MPH OROS was associated with greater persistence rates than MPH IR (12% vs 1%, $p < 0.0001$). There is uncertainty about how well this study population represents patients in actual practice as ethnicity and comorbidity characteristics were not reported.

California Medicaid claims files from a 3-year period were examined in the second study to identify youth prescribed MPH ($n = 11,537$).⁴¹ This study population involved a lower than average proportion of white patients (45.3%) and higher proportions of Hispanic patients (26.1%). Total mean duration (days) of treatment without any 30-day gaps was greater for patients taking ER formulations (combined group of MPH OROS = 83%, MPH ER = 8.7%, MPH SODAS = 8.3%) than for those taking MPH IR (140.3 vs 103.4; survival time ratio (STR) 1.37, 95% CI 1.32-1.42). Subgroup analysis results suggest that persistence duration was

greatest for MPH OROS (147.2 days, 95% CI 142.6-151.7 days) compared to MPH SODAS (113 days; 95% CI 100.9-125.1 days) or MPH CD (101.1 days, 95% CI 91.2-111.0 days). Together, ER formulations extended persistence duration regardless of ethnicity.

Comparisons of SR Formulations

MPH OROS (Concerta®) vs MPH CD (Metadate CD®)

Results from the fair-quality COMACS crossover study of 184 children suggest that relative improvements in SKAMP deportment and attention scale scores differed for the comparison of MPH OROS 18-54 mg and MPH CD 20-60 mg (both given once daily) depending on time of assessment.^{67, 68} This study examined the pharmacodynamic differences of these products resulting from differences in pharmacokinetic profiles. The children were mostly male (73.8%), with a mean age of 9.6 years and they were randomized to low, medium or high dosage treatment group sequences based on their previous dosages of MPH IR. Table 3 below illustrates effect sizes which suggest that MPH CD was associated with significantly larger effect sizes than MPH OROS in the morning, treatment effects were similar in the afternoon, and MPH OROS was superior in the evening. This study presents several problems, however, in that the SKAMP scale has been criticized for lack of sensitivity to change in symptoms, and that ANOVA analysis found the interaction of site x treatment x sequence (the order to randomization within patients) was found to be statistically significant. This finding resulted in the authors conducting additional analyses; however the effect of sequence was not included in these subsequent analyses. Therefore, these findings should be interpreted with caution.

Table 3. Effect sizes for MPH CD and MPH OROS by time of day (COMACS study)

	9:00 am	10:30 am	12:00 pm	2:30 pm	4:00 pm	7:30 pm
SKAMP Deportment						
MCD	.82	.89	.80	.76	.54	.06
CON	.52	.50	.50	.66	.51	.25
SKAMP Attention						
MCD	.70	.72	.66	.65	.50	.00
CON	.41	.48	.42	.64	.53	.20

MPH OROS (Concerta®) vs MPH SODAS (Ritalin LA®)

A small 1-week crossover study of MPH SODAS 20mg versus MPH OROS 18mg and 36mg³⁹ found MPH SODAS superior on the attention or deportment subscores of the Swanson, Kotlin, Agler, M-Flynn and Pelham (SKAMP) scale depending on the time-point and dose comparison. Secondary outcome assessment also found MPH SODAS superior on one measure (proportion correct on math test). These limited differences are mitigated by concerns over the assessment tool (SKAMP) sensitivity, use of a simulated classroom, involvement of study sponsor in authorship, and differences in groups at baseline.

No direct comparisons of other extended release formulations of methylphenidate or other ADHD drugs were found.

Methylphenidate ER (Metadate®) vs Placebo

A 3-week trial of Metadate® versus placebo enrolled 314 children out of 507 screened.⁶⁹ Twenty four percent of those excluded at screening were because they responded to placebo during a 1-week washout period. This biases the study population towards the Metadate® arm,

reducing the applicability of the results. The mean change in the primary outcome measure, the teachers CGI ratings combined, in the morning and afternoon, were significantly lower (better) in the Metadate® group. Secondary measures also favored Metadate®.

Immediate Release Formulations

Dextroamphetamine versus Methylphenidate

Nine fair quality studies (reported in 11 publications) of DEX versus MPH IR.^{33-35, 37, 44-46, 70-73} Two poor quality studies, and one poor-quality sub-group analysis were found.^{27, 74, 75} All nine fair quality studies were randomized, blinded crossover trials. Table 4 summarizes the study characteristics.

Table 4. Dextroamphetamine IR versus Methylphenidate IR Study Characteristics

Study	N, Duration	Diagnosis Criteria	Final Dose*	Results
Efron 1997	N = 125 2 weeks	DSM-IV criteria for ADHD	DEX 0.15mg/kg MPH 0.3 mg/kg	No differences found
Efron 1998	N = 102 2 weeks	DSM-IV criteria for ADHD	DEX 0.15mg/kg MPH 0.3 mg/kg	No differences found
Elia 1990	N = 31 3 weeks	DSM-III criteria for attention deficit disorder with hyperactivity	< 30 kg/ > 30 kg: DEX 40 mg/ 45 mg MPH 70 mg/ 90mg	No differences found
Elia 1991	N = 48 3 weeks	DSM-III criteria for attention deficit disorder with hyperactivity	< 30 kg/ > 30 kg: DEX 40 mg/ 45 mg MPH 70 mg/ 90mg	No differences found
Elia 1993	N = 33 3 weeks	DSM-III criteria for attention deficit disorder with hyperactivity	< 30 kg/ > 30 kg: DEX 40/ 45 mg MPH 70 / 90 mg Placebo	No differences found
Sharp 1999	N = 32 3 weeks 100% Girls	ADHD symptoms present in at least 2 settings; Conners Hyperactivity factor scores at least 2 SD greater than age and sex norms	DEX 0.64 mg/kg MPH 1.28 mg/kg	No differences found
Arnold 1978	N = 29 3 weeks	Diagnosis of Minimal Brain Dysfunction with; total score of 24 or more on the first six items of the David's Hyperkinetic Rating Scale	DEX : 15 mg MPH : 30 mg	No differences found
Kaufman 1981	N = 12 6 weeks	Children diagnosed as "hyperactive," according to a set of predetermined clinical criteria (NR)	DEX 10-60 mg MPH 5-30 mg Placebo	No differences found
Simpson 1980	N = 12 8 weeks	1) Hyperactivity that had been long term; 2) complaints of hyperactivity by parents and teachers; 3) at least average intellectual abilities as measured by the WISC-R.	NR	Post-Hoc analysis: DEX "the most effective drug, where a positive effect was seen"

* All doses divided into morning/noon doses

The two largest studies,^{33, 71} which used clear criteria for diagnosis, enrolled children with ADHD in order to test the hypothesis that some adverse events associated with stimulants are actually characteristics of ADHD and would be improved by drug treatment in one study,⁷¹ and to test the differences between child and parent assessment of therapy in the other.³³ Neither study provides details on the efficacy results, other than summary statements that there were no differences between the two drugs based on children's self-assessment³³ and based on parent and

teacher ratings.⁷¹ These 2 studies had similar populations, primarily children with the Mixed subtype (82%); however co-morbidities and ethnicity are not reported.

Of the 7 small studies (n = 12 to 48), only one found a difference between the drugs.⁴⁶ This study assessed attention to task and deviant behavior in the usual classroom settings using a modified version of the Werry-Quay Direct Observational System.⁴⁶ The text of the paper reports that in a post-hoc analysis, DEX was the most effective drug *in instances where a positive effect was seen*. Because this study did not use a standardized tool for diagnosis, and ADHD subtypes, co-morbidities or ethnicity are not reported, it must be assumed that significant heterogeneity in the population may have lead to the discordant results.

Response Rates

Very few studies attempted to make a comparison of the rate of response (defined a priori) between 2 drugs. Table 5 shows the studies that did. Overall, no differences in response rates, as defined below, were found between the comparisons of MPH OROS, DEX IR, or Amphetamine mixture to MPH IR. Additionally, the majority of these response rates are lower than those reported and quoted from placebo controlled trials (rates of approximately 75%).

Table 5. Comparison of Response Rates to MPH IR

	Interventions	Response Rate Definition	Response rates (% pts)
MPH OROS vs MPH IR			
Pelham 2001 Crossover N=70	MPH OROS MPH IR x 1 week	Parent/teacher ratings of Global Effectiveness as "Good" or "Excellent"	Parent: 67.2 vs 64.7 Teacher: 67.2 vs 57.4
Wolraich 2001 Parallel N = 192	MPH OROS MPH IR x 4 weeks	CGI rated as "much" or "very much" improved Parent/teacher ratings of Global Effectiveness as "Good" or "Excellent"	46.2 vs 47.2 Parent: 54 vs 46.5 Teacher: 42.9 vs 46.9
DEX IR vs MPH IR			
Efron 1998 Crossover N=102	DEX IR MPH IR X 2 weeks	Parental ratings of drug as "very helpful" or "a bit helpful"	62.4 vs 73.5
Efron 1997 Crossover N=125	DEX IR MPH IR x 2 weeks	Parental ratings that child improved overall	68.8 vs 72
Sharp 1999 Crossover N=42	DEX IR MPH IR x 3 weeks	CGI: "very much improved" or "much improved"	85 vs 83
Amphetamine mixture (Adderall) vs MPH IR			
Pliszka, 2000 Parallel N = 40	Adderall: MPH IR x 3 weeks	CGI improvement score of 1 or 2: "very much improved" or "much improved"	90 vs 65; p=0.12

Functional Outcomes

We found extremely limited information on functional capacity outcomes from the clinical trials. Therefore, we included observational studies of ≥ 6 months duration that reported outcomes that reflect functional capacity, for example academic achievement in terms of progression through grades, suicide attempts, police contacts, etc. We found only 2 studies (Evidence Tables 13 and 14).

MPH IR vs MPH OROS (Concerta®)

IHCIS managed care claims' data (described above) suggest that MPH OROS was associated with fewer outpatient visits/hospitalization for accidents/injury than MPH IR over a 12-month follow-up period (Odds ratio 0.58, 95% CI 0.353 to 0.945).⁶⁶ The study population was 75% male, with a mean age of 9.7 years; however, no other information regarding ADHD subtypes, comorbidities, or race/ethnicity were provided.

MPH IR

In a 4-year follow-up study of 62 children treated with MPH, the effect of duration of treatment on academic performance was assessed.⁷⁶ The duration of treatment was divided into < 6 months, 6 months to 2 years, 2 – 3 years, and 3 – 4 years, and those currently taking stimulants at follow-up. No differences were found between the groups on academic achievement as measured by teachers, the proportion repeating grades, in special education classes or being tutored. Although the proportion of children repeating grades was lowest in the group continuing to take MPH (8% vs 46%, 50%36%, 31%) this difference was not statistically significant – possibly because of the small numbers of boys per group (10 to 14). Due to methodological limitations, this study provides no comparative information.

Maintenance of Short-Term Symptom Response Effects**MPH or DEX versus Placebo or Non-drug Therapy**

All of the trials reported above are very short-term trials (range 1 to 9 weeks). Because of this serious limitation, this evidence does not provide information on the long-term benefits of these drugs in treating ADHD. To provide further evidence on duration of effect, and longer-term outcomes, placebo- or non-drug therapy controlled trials of ADHD drugs with duration ≥6 months are reported here (Evidence Tables 7 and 8).

We found 3 placebo-controlled trials of at least 6 months duration, 1 with DEX IR and 2 with MPH IR⁷⁷⁻⁷⁹ and 3 trials that randomized children to stimulant medication or non-drug therapy for 12 to 14 months.⁸⁰⁻⁸² Two studies were poor quality due to serious flaws that represent significant potential for bias. The placebo controlled trial of DEX did not report any baseline characteristics of the two groups, and did not conduct an ITT analysis while the numbers and reasons for withdrawal are also not reported.⁷⁷ A trial of MPH IR, cognitive training or both (n=30) omitted important information about basic information on study design and outcomes (e.g. randomization, baseline characteristics, blinding, and loss to follow up).⁸³

Overall, the MPH IR studies provide a mixed picture of the consistency of efficacy of MPH over 6 months to 2 years. The only study reporting that the short-term effects were maintained over the follow-up period was the Multimodal Treatment Study of Children with Attention Deficit/Hyperactivity Disorder (MTA) study.

The Multimodal Treatment Study of Children with Attention Deficit/Hyperactivity Disorder (MTA) was a relatively large study (n = 579) funded by the NIMH assessing medication management, behavioral treatments, standard community care, and combined medication management and behavioral treatments over a 14-month period.⁸⁰ Outcomes are available for 540 children that were followed an additional 10 months subsequent to trial discontinuation.⁴² Medication management could involve any stimulant medication, but started with MPH titration. At study end, 73% of those in one of the medication management groups

were on MPH, and 10% on DEX, with small numbers of patients taking no medication, pemoline, imipramine, bupropion or haloperidol and 6% refusing to be in the medication arm assigned. All participants met DSM-IV criteria for ADHD combined type, had a mean age of 8.5 years and 80% were males. The sample population was ethnically diverse, with White (61%), African American (20%), and Hispanic (8%) representation. Comorbidities included anxiety disorder (33.5%), conduct disorder (14.3%), oppositional-defiant disorder (39.9%), affective disorder (3.8%), tic disorder (10.9%), mania/hypomania (2.2%) and other (e.g., bulimia, enuresis) (0.2%).

Medication management alone resulted in better scores compared to behavioral therapy for the symptoms of inattention (both parents and teachers) and hyperactive-impulsive symptoms (parent ratings). Medication alone resulted in better scores on all ADHD symptoms than community care, except as measured by a classroom observer. Aggression-ODD symptoms scores were better with medication alone compared to community care in teacher ratings only. Combined therapy (medication and behavioral therapy) was not different to medication alone on any scale. Important to this review of ADHD medications, the effect of medication management was maintained over the 14 month period. This study was a pragmatic trial in that the treatments were given openly (after blinded titration in the 2 drug treatment arms), and participants could refuse the assigned arm, or add or change treatments. In the community care arm, for example, 68% were taking ADHD medications although the mean dose and number of doses per day of MPH was lower in the community care arm than the medication arms. However, the outcome measures were not effectiveness outcomes, so the trial must still be viewed as an efficacy trial that indicates that with careful monitoring of dose and drug regimen, ADHD stimulant medications can reduce symptoms of ADHD over a 14-month period.

Families were contacted 10 months after the end of the 14-month study (24 months post-randomization) to assess longer-term persistence of treatment effects.⁴² A total of 540 of the originally randomized 579 (93%) participated and 10 months after study end; 72% in the medication management alone group, 70% in the combined therapy group, 38% in the behavioral therapy group, and 62% in the community care group were taking medication for ADHD. At 24 months post-randomization, medication alone resulted in better scores on ADHD and ODD symptoms than behavioral therapy and community care. Despite this, analyses of combined outcomes from the medication management alone and combined therapy groups compared to those of the behavioral therapy and community care groups suggest a reduction in the improvement magnitude by half from the 14-month to 24-month timepoints; effect size changes for ADHD symptoms=0.60 vs 0.30 and ODD symptoms=0.39 vs 0.21.

The other earlier trials reported a dissipation of effect over time (Table 6). Although some of these studies do not report mean doses, of those that do the doses used in the MTA study were higher.

Table 6. Maintenance of MPH IR short-term effects

Study	Treatments Duration	Sample Size Mean age (yrs) % Male	Results
Kupietz 1998	MPH IR 0.3, 0.5 or 0.7 mg/kg Placebo x 27 weeks	N=47 9.7 % Male NR	Mean CTRS total ratings worse at Week 27 than Weeks 2 or 14
Ialongo 1993	MPH IR 0.4 or 0.8 mg/kg Multimodal treatment MPH 0.4 mg/kg + Multimodal Placebo Trial=3 months; 9 months follow-up	N=96 8.27 years 77.4%	Short-term gains deteriorated at 9 months
Firestone 1986	MPH IR 22 mg Parent training Both x 2 years	N=73 Mean age NR Gender NR	Conners Hyperactivity Index Scores worsened at 1 (N=52) and 2 (N=30) years

Remission Rates: MPH IR

Three studies assessed the effects of withdrawing MPH IR after periods of treatment.⁸⁴⁻⁸⁶ Two of these were poor quality,^{84, 85} but the third study⁸⁶ included a group of 21 boys who had been treated with MPH for a mean of 1.75 years and randomized to 3 weeks of placebo or MPH. Using the CTRS, this study found that on the Subscale items of hyperactivity and defiance the scores during the placebo period were significantly worse than during the MPH period. No baseline assessments were presented, and the analyses are based on scores at week 3 of each condition only so there is no information about the effectiveness of their pre-existing MPH regimen at baseline. In addition, the effect of order of drug/placebo was not analyzed in this crossover study, so the results must be interpreted with caution.

Other Stimulants**Amphetamine mixture versus Methylphenidate Immediate Release**

Three small, fair quality studies of Amphetamine mixture versus MPH IR were found.^{30, 43, 87, 88} One was a parallel group RCT⁸⁸ while the other two were randomized cross-over trials.^{43, 87, 89} Two additional studies were rated poor quality^{40, 89} due to no description of randomization or concealment of randomization code, no ITT analysis, and high discontinuation rates or no randomization (clinician selected drug) and no blinding of patients or outcome assessors.

The parallel group RCT enrolled 58 children with ADHD and randomized to 3 weeks of Amphetamine mixture, MPH IR or placebo.⁸⁸ The mean doses at the end of study were Amphetamine mixture 12.5 mg/day and MPH IR 25.2 mg/day (divided into morning +/- noon doses for both drugs). No differences were found in the mean IOWA CTRS scores (Inattention/Overactivity and Aggression/Defiance subscales) rated by teachers 4 mornings and afternoons a week, but amphetamine mixture was significantly better on both subscales when morning and afternoon scores were combined. No differences were found in parent ratings. The mean CGI-Improvement score (rated by a blinded psychiatrist) was also significantly lower (better) in the amphetamine mixture group than the MPH IR (final score 1.6 vs 2.35, $p < 0.05$), but the difference in the proportions of responders (90% vs 65%, respectively) did not reach statistical significance. No differences were found on the Conners Global Index or final weight.

The two crossover studies were conducted in the same manner by the same authors, conducted in a summer treatment program.^{30, 43, 87} These short-term studies (6 – 8 weeks) enrolled 21 and 25 children, with a higher prevalence of comorbid oppositional defiant disorder (67% and 52%) than the general population of children with ADHD. The first study found amphetamine mixture to be superior to MPH IR given once daily, while few or no differences were found when comparing to MPH IR given twice daily, based on counselor and teacher ratings. Parent ratings of after school behavior indicated that the addition of a third 0.3mg/kg dose of MPH IR, or the amphetamine mixture 0.3 mg/kg once daily dose lead to the best results based on combinations of parent ratings and child task completion. The results of the second study indicate that on a few measures the low dose (10mg twice daily) of MPH IR was not as effective as the higher dose (17.5 mg twice daily) or either dose of amphetamine mixture (7.5 or 12.5 mg twice daily). Measures where this difference was seen were interruption, conduct problems, negative verbalizations, the daily report card score, and counselor ratings of oppositional defiant scores. No difference in response was seen between the two doses of amphetamine mixture and the higher dose of MPH IR.

Amphetamine Mixture versus Dextroamphetamine

The evidence is limited to a single poor quality study of dextroamphetamine IR versus dextroamphetamine SR versus Amphetamine mixture versus placebo.⁹⁰ No conclusions can be drawn.

Dexmethylphenidate (d-MPH)

Only one of two placebo-controlled studies of d-MPH referred to in the most recent FDA Medical Review (http://www.fda.gov/cder/foi/nda/2001/21-278_Focalin_medr_P1.pdf) has been published.⁹¹ d-MPH was associated with significantly greater mean reductions in Teacher SNAP rating score than placebo ($p=0.004$) after four weeks in a fair-quality trial of 132 children (88% male; mean age=9.8 years) with ADHD of mostly the combined type (64%).⁹¹

A small study of the effects of withdrawing d-MPH after a 6-week titration period was poor quality. No conclusions can be drawn about the comparative efficacy of d-MPH.

Modafinil

A small study of modafinil enrolled 24 children with ADHD.⁹² The study duration was variable, with mean durations of 5 and 6 weeks (placebo and modafinil, respectively). In this study, less than 1/3 had oppositional defiant disorder, or conduct disorder (27% combined), and the ADHD subtype was primarily Mixed (73%). Two children (8%) in the modafinil group were excluded from the analysis because they did not have post-randomization assessments. Modafinil was found better than placebo in improving scale scores, and parent assessments.

Atomoxetine

Atomoxetine versus Methylphenidate

Atomoxetine, the first nonstimulant introduced specifically for ADHD was compared to MPH IR in 3 RCTs.^{93, 94} However, 2 of these studies were really comparisons to placebo, with only few patients enrolled in the MPH arms. Therefore, these are considered placebo-controlled trials, below. The single study comparing atomoxetine and MPH IR found no differences between the drugs based on changes in the ADHD-RS, the CPRS-R hyperactivity item, and the

CGI-S.⁹³ Concerns over the study quality indicating potential bias suggest caution in interpreting these findings (see Evidence Table 4).

Atomoxetine versus MPH OROS

The Formal Observation of Concerta® versus Strattera® (FOCUS) trial compared *open-label* methylphenidate OROS and atomoxetine for three weeks in 1,323 children with ADHD.⁹⁵ Main findings from the FOCUS trial are summarized in Evidence Table 3, but will not be discussed here due to concerns about study quality. The FOCUS trial was rated poor quality based on a combination of flaws including undescribed methods of randomization and allocation concealment, significant between-groups baseline differences in ADHD severity, and lack of information about attrition and number of patients included in analyses (Evidence Table 4).

Atomoxetine versus mixed amphetamine salts XR (Adderall SR®)

The extended release form of mixed amphetamine salts (Adderall SR®) 10-30 mg was superior to atomoxetine 0.5-1.2 mg/kg/day on most efficacy outcomes after three weeks in a fair-quality trial of 215 children (mean age=8.7 years).⁹⁶ This trial, also known as StART (Strattera®/Adderall XR® Randomized Trial), was conducted in a simulated classroom setting which involved 12 hours of observation per day. Participants were mostly male (71.9%) who were diagnosed with ADHD of either the hyperactive/impulsive or combined subtypes. Adderall XR® was associated with significantly greater reductions in the mean SKAMP deportment scale scores, which was prespecified as the primary outcome (-0.56 vs -0.13; $p<0.0001$). Adderall XR® was also associated with superior outcomes on multiple secondary outcome measures including mean change in SKAMP Attention scale scores, proportions of SKAMP scale “responders” ($\geq 25\%$ improvement on Deportment and/or Attention scales), and numbers of math problems attempted and/or completed correctly. One caution regarding the interpretation of these findings is that the SKAMP scale has been criticized for lack of sensitivity to change in symptoms.

Atomoxetine versus Placebo

Six placebo controlled studies of atomoxetine in children and adolescents with ADHD found atomoxetine to be superior based on ADHD-RS as the primary outcome measure and various scales as secondary measures.^{94, 97-100} Results of two of the six trials were described as identically-designed and were reported in one publication.⁹⁴ The mean change on ADHD-RS in these 6 to 9 week studies ranged from -12.8 to -16.7 with atomoxetine compared to -5 to -7.0 for placebo. A study of once daily dosing reported response rates (defined as $\geq 25\%$ reduction in ADHD-RS score), in the atomoxetine group of 59.5% versus 31.3% in the placebo group ($p<0.001$).¹⁰⁰ Remission rates (defined as an endpoint CGI-S score of 1 or 2) were 28.6% and 9.6%, respectively ($p=0.003$). All 5 studies were funded and co-authored by representatives of the manufacturer of atomoxetine, and 4 were part of the NDA submitted to the FDA. All used the DSM IV criteria, however the proportions of ADHD subtypes varied, for example 52 to 79% of enrolled children had the Mixed subtype. More concerning is the variation in the proportions of children with each subtype per assigned group. Proportions of children with co-morbidities also varied across the studies (e.g. 18 to 45% with oppositional defiant disorder). Results of a subgroup analysis from two identically-designed placebo-controlled trials⁹⁴ suggested that atomoxetine was associated with significantly greater reductions in ADHD-RS Total Scores than placebo (-17.0 vs -7.5; $p<0.001$) in 98 of the original 291 children with comorbid ADHD and

oppositional defiant disorder (ODD).¹⁰¹ No analyses based on ADHD subtypes or other comorbidities were reported.

A significantly greater proportion of patients taking once daily dosages of atomoxetine (≤ 1.8 mg/kg/day) responded to atomoxetine than placebo (69% vs 43.1%; $p=0.003$) in a more recent fair-quality trial ($n=153$).¹⁰² “Response” was defined as a 20% or greater mean reduction in total scores from the ADHD-RS-IV-Teacher Version. This trial differs from the previous five in that it was designed with a primary measure of response that was based on teacher reports in the school setting rather than on parent ratings. Children in this trial were predominantly male (80.4%) with ADHD of the Combined type (72.5%) and had a mean age of 9.9 years.

Atomoxetine was associated with less rapid times to relapse than placebo under double-blind conditions (218 days vs 146 days; $p<0.001$) in a randomized subgroup of 416 children (out of 603) that were classified as “responders” following an initial 12-week, open-label period of treatment with atomoxetine.¹⁰⁰ The primary outcome measure was the number of days to relapse and relapse was defined as return to 90% of baseline ADHD-RS score and CGI-S score increase of at least 2 points. Similarly, fewer patients on atomoxetine relapsed than on placebo (22% versus 38%, $p<0.002$).

Adolescents (ages 13 to 17)

Evidence on the effectiveness of pharmacotherapy for ADHD in adolescents is very limited (Evidence Tables 1 and 2). We did not find any effectiveness trials or long-term observational studies (assessing functional or safety outcomes) in adolescents with ADHD. Adolescents were studied in one head-to-head trial of MPH IR and SR (OROS)⁶⁰ and in 9 placebo-controlled trials of MPH.¹⁰³⁻¹¹² Mixed age populations including adolescents were studied in efficacy trials of atomoxetine, however data are not stratified by school age and adolescents and so are considered in the school-age children section (above).

Direct comparisons

MPH IR vs MPH OROS (Concerta®)

A single, very small, *single blinded* crossover study of 6 adolescent boys showed MPH (OROS) superior to MPH IR on some simulated measures of driving skills, dependent on the time of day of testing.⁶⁰ ADHD was confirmed using the DePaul ADHD Rating Scale IV (parents completed), the Diagnostic Interview Schedule for Children (DISC-IV), and the Standardized Interview for Adult ADHD. Four of the 6 had inattentive type ADHD. After 7 days of dosing, the teens performed significantly better while taking MPH OROS on 3 of 9 measures (inappropriate braking, missed stop signals, and speed control) at each testing time (2 pm, 5 pm, 8 pm, and 11 pm). Because only F and P-values are reported, it is not possible to interpret the magnitude of differences found. An analysis of a combined score of 7 (of 9) measures at each of the 4 time points indicated that there were no differences between the formulations at the 2 pm and 5 pm test times, but the scores were significantly lower with the IR formulation at the 8 pm and 11 pm times ($p<0.01$). Self-evaluations of risky driving behavior did not show any differences between the formulations. Adverse events were not measured. Since 2 teens were previously on MPH OROS, and 2 had been taking MPH IR, and the only person blinded was an observer in the driving simulator, it would be important to know the effect of prior medication and order of randomization. These were not assessed.

Indirect comparisons

Placebo-controlled trials in adolescents only involved assessments of MPH IR and do not offer opportunities for indirect comparisons. Seven placebo-controlled crossover trials of MPH IR enrolled a total of 171 adolescents.^{103-111, 113, 114} Patients were diagnosed primarily using the DSM III-R or DSM-IV criteria. Only one trial clearly described the distributions of the different ADHD subtypes and in this trial there were 87.5% patients with the Combined subtype.¹¹⁴ MPH IR generally was superior to placebo in improving core ADHD symptoms, but was associated with greater frequency of appetite and sleep problems. MPH mean dosages ranged from 8.8¹⁰³ to 75 mg.¹⁰⁸ The trials reported a variety of outcome measures. All but one were consistent in using various forms of the highly valid Conners' rating scales (long- and abbreviated forms).¹¹⁴ However, inconsistency in the way results are reported make estimation of an overall magnitude of effect impossible.

Functional Outcomes: MPH IR

We found extremely limited information on functional capacity outcomes from the clinical trials. Therefore, we included observational studies of ≥ 6 months duration that reported outcomes that reflect functional capacity, for example academic achievement in terms of progression through grades, suicide attempts, police contacts, etc. We found only 2 studies reporting outcomes in adolescents. In an uncontrolled study, a simple follow-up of 16 of 27 (59%) adolescents who had responded to MPH in an uncontrolled study,¹¹⁵ after 6 to 14 months of follow-up the authors simply report that 15 of the 16 had "improved grades".

In a study using interviews and data from patient charts, 97 young adult males who had taken MPH as children and teens (mean age at discontinuation of MPH was 17 years) were studied.¹¹⁶ There is no comparison group in this descriptive study. The authors conducted a hierarchical analysis to assess the effect of various factors. Significant findings relating to use of MPH were: fewer suicide attempts positively associated with higher dose of MPH and emancipated living situation, and level of relationship commitment were positively associated with response to MPH. Early response to MPH was negatively associated with high school graduation, however.

Adults

Treatment of ADHD in adults has not been widely studied. Only one of three previous, good-quality systematic reviews included studies of adult ADHD.⁵ There were few studies of only DEX, MPH IR and pemoline in adults available at the time of the Jadad review (1999).⁵ Jadad et al criticized these studies for their small sample sizes, short durations (≤ 6 weeks) and for incomplete reporting methods. The review included one study of DEX and MPH¹¹⁷ and placebo-controlled studies of MPH,¹¹⁸⁻¹²⁰ pemoline¹²¹ and other drugs not included in our review. Jadad et al did not draw any conclusions from the study of DEX and MPH because no direct comparisons of these drugs were reported, only changes from baseline.¹¹⁷ They reported that MPH's efficacy in reducing core ADHD symptoms was inconsistent across placebo-controlled trials and that pemoline was not associated with overall symptom improvement.

Subsequent to the Jadad et al review, other studies have been published that expand the evidence base for DEX,¹²²⁻¹²⁴ MPH¹²⁵⁻¹³⁴ amphetamine mixture,¹³⁵ atomoxetine^{136, 137} and modafinil.^{122, 138} These are included and reviewed here. These studies were fair quality, with

one exception.¹³⁴ The most recent study of MPH is poor quality due to serious concerns about the validity of the outcomes in light of unsuccessful randomization (method not described, but uneven distribution of age) and uncertainty about characteristics of the groups analyzed (not an ITT).¹³⁴

Direct comparisons

One head-to-head trial was published subsequent to the Jadad et al review (Evidence Tables 9 and 10).¹²² Identical proportions of adults (n=22) with ADHD responded to modafinil 206.8 mg and DEX IR 21.8 mg (48% vs 48%; p=NS). Response was defined as a 30% or greater mean improvement in ADHD Rating Scale total scores. Patients in this trial were mostly male (59%) and had a mean age of 40.8 years.¹²²

Indirect comparisons

Placebo-controlled trials were conducted to evaluate whether adults with ADHD benefit from the same treatments that are used in children.^{118-121, 124, 126-133, 135-143} All but two trials were rated fair-quality.^{134, 143} The two poor quality trials were characterized by inadequately described randomization and allocation concealment methods and between-groups differences at baseline and excluded patients from outcome analyses.^{134, 143} Only half of the fair-quality trials quantified response rates (Table 7). The rates were variable, even within drug or within method of assessing response: amphetamine mixture=70.4%,¹³⁵ atomoxetine=52.4%,¹³⁶ DEX=58%,¹²⁴ and MPH IR=38-78%.^{119, 120, 128, 133, 142}

These placebo-controlled trials fail to provide conclusive evidence about indirect comparative efficacy. It is impossible to attribute differences in response rates to variations in drug effects due to the heterogeneity in design characteristics found across these studies. The wide range of placebo response rates reported (0 – 37%) evidences this heterogeneity.

Sources of heterogeneity include study duration (2-13 weeks), medication dosage levels, response measurement methods, and, most importantly, populations. The primary source of population heterogeneity is variation in ADHD diagnosis methods. Studies differed in ADHD diagnosis methods with regard to usages of diagnostic criteria (Utah criteria, DSM-III-R, or DSM-IV), requirement of second reporter corroboration (i.e., family member), and symptom severity thresholds (e.g., various measurement scale cut-off scores). Studies with more rigorous diagnostic methods^{122, 128, 133, 140} may be characterized by patients with homogenous symptom presentations; whereas, studies with less stringent criteria^{120, 121, 124, 141, 142} may be more representative of the average patient.

Other potential sources of population and response differences include distribution of ADHD subtypes and presence of co-existing illnesses. Few studies reported prevalence rates of Inattentive (37-58%), Combined (35-63%) and Hyperactive-Impulsive (0-9%) subtypes.^{122, 124} Differing subtype prevalence patterns cannot be ruled out in studies that didn't report this information.^{119-121, 125, 128, 133, 135, 136, 140-142} Few trials reported prevalence rates of "any comorbidity" (range=22-78%) and mood/anxiety disorders (range=4.5-68%).^{119, 120, 128, 135, 136, 141, 142} One study focused entirely on patients with ADHD and comorbid cocaine dependence.¹²⁸ Few studies examined the roles of ADHD subtypes or comorbidities in accounting for drug effects. Those that did reported a lack of adequate statistical power to detect differences and

found similar response rates for atomoxetine in patients with inattentive and combined subtypes¹³⁷ and for atomoxetine in patients with comorbidities.¹³⁶

Table 7. Adult ADHD - Response Rates from Placebo-Controlled Trials

Drug	Study Sample Size	Dosage (mean) x Duration (weeks)	Response Rates
Adderall	Spencer 2001 N=27	53.7 mg x 3	70.4% vs 7.4%, p<0.001 ^A
Atomoxetine	Spencer 1998 N=21	76 mg x 3	52.4% vs 9.5%, p<0.01 ^A
DEX	Paterson 1999 N=45	23.85 mg x 6	58% vs 0; p<0.001 ^B
MPH IR	Wender 1985 N=37	43.2 mg x 2	57% vs 11%; p<0.0001 ^D
	Bouffard 2003 N=30	30-45 mg x 4	63% vs NR, p=NR ^E
	Schubiner 2002** N=48	90 mg (max) x 13	77% vs 21%; p<0.05 ^E
	Spencer 1995 N=23	0.92 mg/kg x 3	78% vs 4%; p<0.001 ^A
	Kooij 2004 N=45	0.91 mg/kg x 3	38% vs 7%; p=0.003 ^F

A: ≥ 30% reduction in ADHD Rating Scale

B: CGI score=1 ("much") or 2 ("very much") improved

C: A or B

D: Moderate to marked improvement on Physician's Global Rating Scale

E: Other/Unspecified

F: A and B

** Patients comorbid for Cocaine Dependence

Results were contradictory in placebo-controlled trials of MPH that measured core ADHD symptom improvement using a variety of, or unspecified assessment methods.^{118, 126, 127, 129}

Evidence regarding treatment effects on quality of life and other ADHD-related symptoms (depressed mood, anxiety, and cognition) is not compelling (Table 8). Atomoxetine improved functional status more than placebo (Sheehan Disability Scale Overall Score -4.5 vs -2.9, p=0.022) in one study but this was not replicated in another (-4.4 vs -4.0, p=NS).¹³⁷ MPH IR generally reduced symptoms of anxiety (HAM-A, Beck Anxiety, POMS)^{120, 127, 133, 142} and improved cognition as measured by the CPT or CPALT.^{127, 130, 131, 133, 140, 141} MPH SR improved depressive symptoms (POMS) after 4 weeks in 37 patients.¹²⁹ No differences were found between single doses of MPH IR 10 mg, 20 mg and placebo in simulator driving performance in 52 adults with ADHD (74% male; 31.3 years).¹⁴⁰

Table 8. Adult ADHD – Other symptom-related outcomes in PCTs

Drug	Trial	Dose (mean) x Duration (wks)	Sample Size % male	Effective in treating: Depressive Symptoms	Anxiety Symptoms	Cognition
Atomoxetine	Spencer 1998	76 mg x 3	N=21 48%	-	-	Yes
	Michelson 2003*	94 mg/day x 10	N=536 65%	No	No	-
DEX	Paterson 1999	24 mg/day x 6	N=45 60%	No	No	-
MPH IR	Bouffard 2003	30-45 mg (tid) x 4	N=30 80%	No	Yes (HAM-A)	Yes (CPT)

Drug	Trial	Dose (mean) x Duration (wks)	Sample Size % male	Effective in treating:		
				Depressive Symptoms	Anxiety Symptoms	Cognition
	Gualtieri 1985	0.3 mg/kg (bid) x 5 days	N=8 100%	-	-	Yes (CPT)
	Kinsbourne 2001	5, 10, or 20 mg/day (QD) x 1 day	N=17 41%	-	-	Yes (CPALT)
	Tenenbaum 2002	45 mg/d (max; qid) x 3	N=24 46%	No	Yes (Beck Anxiety)	Yes (CPT)
	Wender 1985	43 mg x 2	N=37 54%	Yes (POMS)	Yes (POMS)	-
	Kooij 2004/Boonstra 2005	0.91 mg/kg x 3	N=45 53.3%	No	No	Yes (CPT)
	Barkley 2005	MPH 10 mg MPH 20 mg	N=52	-	-	Mixed (CPT)
MPH SR	Levin 2002	20 mg/day x 4	N=347 63%	Yes (POMS)	-	No
Modafinil	Turner 2004	200 mg x single dose	N=20 65%	-	-	Mixed (Various)

*2 studies reported together

Functional Outcomes: MPH IR

We found extremely limited information on functional capacity outcomes from the clinical trials. Therefore, we included observational studies of ≥ 6 months duration that reported outcomes that reflect functional capacity, for example academic achievement in terms of progression through grades, suicide attempts, police contacts, etc. We found 2 studies that reported these outcomes among adult patients who had been treated as children^{76, 115, 116, 144, 145}. Due to various methodological limitations, these studies do not provide good evidence for long-term effectiveness even for MPH.

In a cross-sectional follow-up study of young men diagnosed with ‘persistent hyperactivity’ at ages 6 to 12 years, those who had not received medication were compared to a group that had received MPH for at least 3 years during childhood.¹⁴⁵ The groups were initially seen in different time-periods, separated by 5 to 15 years. Because the groups were from different periods, a third group of normal children who were contemporaneous to the MPH group was added. The sizes of the groups also differed, with 64 in the non-treated hyperactive group, 20 in the MPH treated group, and 20 in the normal controls and data were not available for all subjects on all questions. Mean follow-up of the hyperactive groups was 10 to 12 years. No information on baseline characteristics from childhood is given. No consistent differences in functional outcomes were found between the MPH and untreated groups (Table 9). Considering the potential confounding of differences in the years the children were treated, and the very small numbers of subjects per group per variable, these results should be interpreted with caution.

Table 9. Long-term functional outcomes of MPH from Hechtman 1984

Variable	Favors	MPH group	Non-treated	p-value
Age at follow-up	NA	22 years	20 years	<0.01
Living with girlfriend/wife (n)	MPH	8	5	<0.01
Duration last job held	Non-treated	21 weeks	70 weeks	<0.001
Aggression	Untreated			<0.06
Psychiatric treatment at present	MPH	1	22	<0.02
Age starting alcohol use	Non-treated	14.8 years	16.2 years	<0.03

Variable	Favors	MPH group	Non-treated	p-value
Duration of alcohol use	Non-treated	25 months	10.8 months	<0.05
Abuse/addiction to alcohol (n)	MPH	13	26	<0.05
Age at first cocaine use	MPH	20 years	18.9 years	<0.02
Age stopping cocaine use	Non-treated	22 years	18.9 years	<0.001

The MPH group in this study was previously reported after 5 years of follow-up (as adolescents), with comparison groups of boys treated with chlorpromazine or untreated boys.¹⁴⁴ This study reported academic performance, with no differences found between the groups.

Key Question 2: Safety.**What is the comparative tolerability and safety of different pharmacologic treatments for attention deficit disorders?*****Short-Term Trial Evidence in Young Children (Preschool Age; 3-5 years)***

One of three placebo-controlled trials of MPH IR reported results of adverse event assessments.⁵¹ MPH IR was clearly associated with higher rates of increased sadness, decreased appetite, and sociability impairments than placebo after 7-10 days in 31 preschoolers.

Short-Term Trial Evidence in Children (Elementary School Age; 6-12 years)

Adverse events were reported in 17 head-to-head trials. The results are summarized in Table 11 below, full reporting of adverse event data can be found in Evidence Table 3.

Stimulants

Four of six trials of DEX versus MPH IR reported no differences between the drugs in adverse events.^{35, 70-72} However, 2 short-term crossover trials found DEX to cause greater weight loss than MPH IR with mean weight change differences of 0.7 kg to 0.97 kg.^{45, 73} One of 3 trials of Amphetamine mixture versus MPH IR found no difference in adverse event rates,⁸⁸ but 2 other studies found differences.^{43, 87} Limitations in study design and lack of description of analysis methods make results from these studies less reliable. These studies found that adding additional doses to the daily regimen of either drug increased the reports of loss of appetite and sleep problems,⁸⁷ and that Amphetamine mixture given twice daily caused the highest rates of these adverse events.⁴³ All 3 studies of MPH IR versus extended release formulations (MPH OROS, MPH SODAS, and MPH SR) that reported no significant differences in the incidence of side effects.^{59, 61, 62} Amphetamine mixture and DEX SR were found to cause more weight loss than DEX IR during the first week of treatment, but weight gain during the second week was greater with these drugs than with DEX IR.⁹⁰ Since this was such a short-term trial, no conclusions about differential effects on weight can be made from these data. No differences in adverse event rates were found between MPH SR (Ritalin LA®) and MPH OROS (Concerta®)³⁹ or between MPH CD (Metadate CD®) or MPH OROS (Concerta®).⁶⁴

Comparisons to atomoxetine

Atomoxetine caused significantly more vomiting and somnolence than both MPH IR⁹³ and Adderall XR®⁹⁶ in two trials. Atomoxetine was associated with lower rates of 'abnormal thinking'⁹³ than MPH IR and lower rates of insomnia Adderall XR®.⁹⁶

Table 10. Summary of Adverse Effects Reported

Study	Differences Found	Study	No Differences Found
DEX versus MPH IR			
Kauffman 1981 Crossover; N=12 6 weeks	Significant difference found only on weight change: Mean change in weight (kg): DEX -0.86 vs MPH +0.11 (Difference 0.97kg, p NR)	Arnold 1978 Crossover; N=29	P = NS (incidence and weight change)
Sharp 1999 Crossover; N=32	Mean change in body weight (kg) reported to be greater with DEX. Difference 0.7 kg Dextroamphetamine: -1.1; p=0.01 from baseline Methylphenidate: -0.4; p=NS from baseline	Efron 1997 Crossover; N=125	P = NS for all (incidence only)
		Elia 1991 Crossover; N=48	P = NS (incidence and severity)
		Elia 1993 Crossover; N=33	P = NS (incidence)
Adderall versus MPH IR			
Pelham 1999a Crossover; N=21	Authors assessment notes that adding an afternoon dose of either drug resulted in increased reports of loss of appetite or sleep delay. Statistical comparison NR.	Pliszka 2000 Parallel; N=58	All p=NS (incidence only)
Pelham 1999b Crossover; N=25	Authors note that differential side effects were seen only for loss of appetite and trouble sleeping with the high (12.5mg/day) dose of Adderall. (p-values NR).		
IR versus SR formulations of MPH			
		Pelham 2001 Crossover; N=70	P = NS ((incidence only)
		Wolraich 2001 Parallel; N=312	P = NS (incidence only)
		Whitehouse 1980 Parallel; N=34	P = NS (incidence only)
Extended release formulations of MPH			
		Lopez 2003 Crossover; N=36	P = NS (% with at least 1 AE)
		Swanson 2004 Crossover; n=214	P = NS (Parent ratings of side effects on the Barkley Scale)
Atomoxetine			
Kratochvil 2002 Parallel; N=228	Atomoxetine vs MPH IR; p=NS on 24 of 27 AEs reported; Atomoxetine worse: Vomiting: 22 (12%) vs 0, p=0.017 Somnolence: 20 (10.9%) vs 0, p=0.029 MPH IR worse: Thinking abnormal: 0 vs 2 (5%); p=0.031		
Wigal 2005 Parallel N=203	Atomoxetine vs Adderall XR®; p=NS on 8 of 11 AEs reported Atomoxetine worse: Vomiting: 4.7% vs 13%; p=0.035 Somnolence: 4.7% vs 18.5%; p=0.0015 Adderall XR® worse: Insomnia: 28% vs 7.4%; p<0.0001		
Multiple Comparisons			
James 2001 Crossover; N=35	Based on SERS assessment tool: ANOVA analysis indicates Adderall and DEX SR caused greater decreases in weight than DEX IR, however these groups also had greater recovery of weight during the 2 nd week (compared to DEX IR in each case). All other findings p = NS for drug vs drug comparisons.		

Growth Effects

A study of withdrawing MPH IR during summer months versus not withdrawing assessed the effect on weight and height.¹⁴⁶ Children with cross-situational, pervasive hyperactive behavior (n = 62) were randomized and followed for a 3 year period. Overall, 42% of those randomized withdrew, with data available for 58 children at the end of summer 1 (ON n=32, OFF n=26); and 34 at the end of summer 2 (ON n=20, OFF n=14). Weight and height were collected by *unblinded* secretaries, but not for the purposes of this study. Both groups gained in weight and height over each summer, but during summer 1, the MPH IR ON group gained significantly less (0.9 kg, p=0.005) than the MPH IR OFF group. However, in summer 2 the difference was non-significant (0.6 kg). The effect on height was the reverse of these finding, with no significant difference in summer 1 (0.1 cm), but a significant difference after summer 2 (1.3 cm, p=0.02). The serious limitations of this study, in design and conduct, limit the likelihood that the findings are valid.

Adolescents

Placebo-controlled trials of MPH IR^{103-113, 147} provide limited evidence of short-term stimulant tolerability in adolescents. MPH IR was associated with significant appetite and sleep disturbances across some, but not all placebo-controlled trials.^{105, 106, 109, 112} Additionally, adolescents taking MPH IR frequently reported increases in dulled affect, social withdrawal, irritability and stomachache in two placebo-controlled trials.^{108, 112}

Adults

There is considerable interest in alternative, nonstimulant treatments for ADHD to address the needs of individuals intolerant of adverse effects that are often associated with stimulants (e.g., insomnia, appetite suppression). Therefore, this review particularly addresses the important question of how atomoxetine and stimulant treatments compare in adverse effects.

In summary, randomized controlled trials do not provide evidence that any one stimulant is more tolerable than another or that atomoxetine is more tolerable than stimulants. Trials were short-term in duration and heterogenous for types of adverse events measured. Adverse events were inadequately defined and ascertainment methods were unclear.

Direct comparisons of stimulants vs nonstimulants

Modafinil and DEX IR were associated with similar rates of insomnia (38% vs 19%, NS), muscle tension (24% vs 19%, NS) and appetite suppression (24% vs 19%; NS) in the only included head-to-head trial.¹²² There were no withdrawals due to adverse effects.

Indirect comparisons

Heterogeneity in design characteristics (discussed above) and in adverse effects measurement and reporting methods prevents reliable indirect comparisons of tolerability across placebo-controlled trials of stimulants and nonstimulants (Evidence Table 11). Table 11 reflects placebo-controlled trials that reported rates of adverse events commonly associated with stimulant therapy, as well as withdrawals. The rates of insomnia and appetite loss in the placebo

groups in these trials varied widely. There were no consistent differences in insomnia or appetite loss across two trials of MPH IR.^{128, 142} Overall, more patients taking atomoxetine withdrew due to adverse events than in the placebo group (8.5% vs 3.4%; $p=0.03$). These findings suggest that atomoxetine may not offer an advantage in tolerability over stimulants with regard to insomnia and appetite loss. However, it may be that the lack of finding a significant difference with the other drugs was due to inadequate sample sizes.

Table 11. Specific Adverse Events in placebo-controlled trials of adults

Trial	N Mean age (yrs) % male	Treatment (mean) x Duration (wks)	Insomnia	Appetite Loss	Withdrawal due to AEs
Stimulants					
Spencer 2001 ¹³⁵	N=27 38.8 years 56%	Amphetamine mixture 53.7 mg x 3	37 vs 14.8% (NS)	29.6 vs 11.1% ($p=0.03$)	-
Schubiner 2002 ¹²⁸	N=48 37.5 89.6%	MPH IR 90 mg x 3	63% vs 33%; $p<0.05$	50% vs 25% (NS)	0 vs 4.2% (NS)
Kooij 2004 ¹⁴²	N=45 39.1 years 53.3% male	MPH IR 0.91 mg/kg x 3	33% vs 22%; $p=0.27$	22% vs 4%; $p=0.039$	None
Atomoxetine					
Michelson 2003 ^{137*}	N=536 41.1 years 65%	Atomoxetine bid 94.4 mg x 10	20.8 vs 8.7% ($p<0.001$)	11.5 vs 3.4% ($p<0.001$)	8.5% vs 3.4%; $p=0.03$

*pooled results from 2 trials

Evidence on the Long-Term Safety of drugs used to treat ADHD

We included observational studies for analysis of long-term safety parameters.^{131, 148-164}

Seven studies used cohort designs to compare groups taking MPH to DEX,^{153, 154, 161, 163} imipramine,¹⁵¹ unmedicated hyperactives,^{161, 162} and general population growth chart norms.¹⁵² Eleven non-comparative studies involved patients exposed to MPH IR,^{131, 149, 150, 156, 157, 159} MPH SR (OROS),¹⁵⁸ atomoxetine,^{148, 153, 164} or Adderall.¹⁶⁰

All but two studies were 1-5 years in duration.^{131, 149} All but one study involved elementary school-aged children.¹⁶⁰ The exception was one before-after study of amphetamine mixture in adults with ADHD.¹⁶⁰

Growth (height and weight) was commonly reported in these studies. Other long-term safety outcomes were assessed, including tics, seizures, cardiovascular adverse events, injuries, and attempted suicide.

No study was rated good quality. All but one was rated fair quality due to biased patient selection processes and/or biased or unspecified outcome ascertainment methods. We did not analyze results from a poor-quality, comparative study of growth rebound in MPH and DEX due to our concerns about how possible additional biases may have affected the results.¹⁶³ We cannot rule out the possibility of between-groups differences in baseline characteristics because no information/analysis was provided. We also cannot rule out the possibility that the results were confounded by time and other relevant factors.

Height and weight effects

A frequently cited nonsystematic review concluded that effects on weight and height associated with MPH IR vary across short-term clinical trials and long-term observational studies and are mostly transient.¹⁶⁵ We reached similar conclusions based on our analysis of a larger number of primarily long-term observational studies that compared MPH IR to DEX IR,^{154, 155, 161} imipramine,¹⁵¹ or unmedicated hyperactive control groups^{157, 161, 162}. Height and weight changes associated with MPH IR^{150, 152, 156, 158, 159} and OROS were also observed in long-term noncomparative studies.¹⁵⁸ A noncomparative study of amphetamine mixture (Adderall XR®) found a low overall rate of withdrawal due to weight loss (4.8%), however weight loss was the most common reason for withdrawal from this 24-month extension of placebo-controlled trials¹⁶⁶

Comparative studies

Height. These studies do not answer the question of whether any one stimulant suppresses growth in height any more than any other, nor do they clearly support a relationship between MPH and suppression of height.

The only comparative evidence comes from two studies of DEX and MPH.^{154, 161} Results are mixed across these studies (Table 12). Both reported changes in height percentiles using the outdated Iowa City norms. DEX and MPH were both associated with similar height *increases* at final follow-up (mean 6 years) in one study,¹⁵⁴ and DEX was associated with significantly greater height *decreases* than MPH after at least two years in the other.¹⁶¹ It is impossible to establish whether heterogeneity in group characteristics across studies may possibly contribute to the contradictory findings, as one of the studies did not report mean age, dosage, or duration.¹⁶¹

Weight. Results from three comparative studies suggest that DEX is associated with significantly greater suppression of weight gain than MPH, at least in the first 1-2 years (Table 13).^{154, 155, 161} DEX was associated with a significantly lower mean weight gain (kg) than MPH after nine months in one study¹⁵⁵ and significantly greater declines in weight percentiles after the first of 5 years in one study¹⁵⁴ and at end of treatment (≥ 2 years) in another.¹⁶¹ In the 5-year, partly retrospective and partly prospective study that involved 84 children (mean age at initiation of drug therapy=9 years and 82% male), however, differences in decreased weight percentiles between DEX and MPH resolved by the second year and resulted in significantly greater than expected mean increases in weight percentiles at final follow-up (+10.9, $p<0.01$ and +12.8, $p<0.001$, respectively).¹⁵⁴

The 9-month study also reported a few subgroup analyses.¹⁵⁵ The first suggests that comparison of mean weight gain between DEX and MPH may have been confounded by dosage disparities. Apparently, the difference between DEX and MPH resolved when four patients taking lower-dose MPH (20 mg/day) were removed from the analysis (0.13 vs 0.12 kg per month). Also, weight gain in children who continued medication over the summer versus those who discontinued medication during the summer was also reported. In patients taking DEX, medication continuation was associated with significantly lower mean weight gain than in children who discontinued medication (0.14 vs 0.47 kg per month, $p<0.01$). Medication continuation status did not have an effect on weight gain in the group of patients taking MPH.

MPH was associated with decreases in weight percentiles similar to imipramine after one year¹⁵¹ and absolute weight changes that were similar those in unmedicated healthy controls in another 2-year study.¹⁵⁷ Results were mixed across two studies that compared children taking MPH to unmedicated hyperactives, however.^{151, 162} In one study, MPH was associated with

significantly greater declines in weight percentiles than in the unmedicated children after one year.¹⁵¹ The differences between the MPH groups and the unmedicated group increased numerically along with the dosages (< 20 mg= -6.88, 20.56 mg= -8.81, > 20 mg=-15.40, all $p<0.005$). In the other study, the MPH group and the unmedicated group demonstrated similar absolute weight gain (kg) after 364 days.¹⁶²

Table 12. Long-Term Height and Weight Outcomes in Observational Studies

Study	Interventions (mean dose) x duration Sample size	Age Gender Population	Height	Weight
Gross 1976	DEX 16.5 mg, n=12 (average follow-up=6.8 yrs) MPH 34 mg, n=60 (average follow-up=5.8 years)	Mean age=9 82% male Children/adolescents with hyperkinetic syndrome or minimal brain dysfunction	Change in percentile: +10.9, $p<0.01$ vs +12.8, $p<0.001$	Change in percentile: +16.0, $p<0.02$ vs +11.4, $p<0.001$
Safer 1972	MPH 37.5 mg, n=4/24.0 mg, n=5 DEX 11.7 mg, n=3/11.8 mg, n=8 x 9 months	Mean age=9.8 Gender NR	NR	Weight gain (kg): 0.23 vs 0.12, $t=1.8$, $p<0.05$ Weight gain (excluding patients taking low- dose MPH, n=16) (kg): 0.13 vs 0.12, $t=0.137$, NS ON vs OFF Weight gain (kg) over a 3-month summer period: MPH= 0.29 vs 0.41, $t=0.526$, $p=NS$; DEX= 0.14 vs 0.47, $t=2.523$, $p<0.01$
Safer 1973	DEX, n=29 MPH, n=20 Unmedicated controls, n=14 x ≥ 2 years Mean dosages NR	Mean age NR 89.8% male in children on medication; 100% male in unmedicated control group 100% white	Change in percentile points: DEX: -13.45 MPH high-dose (> 20 mg): -9.40 All MPH: -5.20 MPH low-dose (≤ 20 mg): -1.00 Controls: +1.29 DEX > MPH all-dosage, low-dosage and control groups, but DEX=MPH high-dosage group; MPH high-dosage > controls; MPH all-dosage and low- dosage=controls	DEX; MPH: high-dose (> 20 mg), all, low- dose (≤ 20 mg); controls Percentile changes in: Weight: -20.38; -10.0, - 6.35, -2.7, +6.79 DEX > all MPH dosage groups and controls; MPH high-dose and all doses > controls; MPH low-dose=controls

Study	Interventions (mean dose) x duration Sample size	Age Gender Population	Height	Weight
Quinn 1975	Condition 1: Imipramine 65.4mg, n=12 Condition 2: MPH 20.56 mg, n=23 Condition 3: MPH > 20 mg a day (n=5) Condition 4=MPH 20 mg a day or less (n=18) Condition 5=No treatment, n=12 x 1 year	Mean age NR 100% male Hyperactivity	Height changes (percentile scores): -2.20 vs +3.19 vs -3.0 vs +5.12 vs -1.46 t-scores for comparisons of condition 5 with 1; 2; 3; 4 (p-values all NS): 0.23; 1.05; 0.22; 1.59 t-scores, p-values for comparisons of condition 1 with 2, 3, and 4: 1.25, p=NS; 0.12, p=NS; 1.90, p<0.05	Weight change (percentile): -7.54 vs - 8.81 vs -15.40 vs -6.88 vs +1.61 t-scores, p-values for comparisons of condition 5 with 1; 2; 3; 4: 2.45, p<0.01; 3.42, p<0.005; 4.18, p<0.005; 3.44, p<0.005 t-scores, p-values for comparisons of condition 1 with 2; 3; 4: .37, p=NS; 1.27, p=NS; 0.19, p=NS
McNutt 1976	MPH vs nonmedicated vs controls 12 months: n=28, n=24, n=47 24 months: n=13, n=10, n=14	<u>12-month</u> 10.2 years 77.8% male <u>24-month</u> 9.9 years 86.5% male Hyperactivity	Medicated hyperactives=controls at 1 and 2 years (data NR) Medicated hyperactives vs unmedicated hyperactives: data NR	Medicated hyperactives=controls at 1 and 2 years (data NR) Medicated hyperactives vs unmedicated hyperactives: data NR
Zeiner 1995	Medicated (MPH 23 mg) vs unmedicated x 1.7 years	mean age 9.0 yrs 100% male Ethnicity NR	Height change (cm): +12.1 vs +12.1 Height at end of treatment (cm): 150.4 vs 148.3; p=NS	End of study measurements: Weight (kg): 42.0 vs 40.3; p=NS

Noncomparative studies

Multiple noncomparative study findings provide inconclusive evidence regarding MPH IR effects on children's height and weight. A pooled analysis of data from open-label extensions of 13 trials of atomoxetine assessed the effect on height and weight.¹⁴⁸

Height. In summary, studies of children taking MPH IR at various doses for 1-4 years showed inconsistent suppression of growth in height as compared to children taking imipramine,¹⁵¹ those who were unmedicated,^{151, 157, 162} and in noncomparative studies that reported varied analyses including differences between expected and actual growth,¹⁵⁰ change in percentile,¹⁵² percent of expected growth,¹⁵⁶ and proportion of patients with decreased growth rates.¹⁵⁹ A before-after study followed 407 children with ADHD taking MPH SR (OROS) 41 mg/day for 12 months. MPH SR was associated with a steady increase in mean absolute height of 5.2 cm. No comparisons to norms or controls were made.¹⁵⁸

Weight. Noncomparative studies^{150, 152, 156, 159} provide mixed evidence about the association between MPH and suppression of weight gain. In the earliest study (1977), only 2 of 36 boys with minimal brain dysfunction (5.5%) gained weight while taking MPH (max dose 20 mg) over 16 months.¹⁵⁹ The other 34 boys gained weight. The next study, published in 1979, involved 72 boys (age range 6-12) with hyperactivity that were taking MPH for up to two years.¹⁵⁶ A significant growth weight deficit (30%, p<0.05) was associated with MPH 24.2 mg/day (0.47 mg/kg) in the 72 boys who completed the first year. The growth weight deficit

associated with MPH 0.59 mg/kg of 10% was insignificant for the 48 boys who completed the second year of treatment. Results of a subgroup analysis suggest that the deficit in weight gain was only significant in patients that continue to use medication over the summer months compared to those who did not. The third study, published in 1983, involved relatively higher mean dosages of MPH (39.9 to 41.3 mg) and followed children with hyperactivity over the longest observation period (4 years).¹⁵² MPH was associated with significant declines in weight percentiles in all four years of the study (Years 1: -9.7 vs 2: -15.9 vs 3: -18.6 vs 4: -20.8; $p < 0.001$ for all). The final study, published in 1999, found an insignificant difference (0.72 kg) between expected vs actual weight gain in 29 patients who took MPH 34.5 mg for two years.¹⁵⁰

In a before-after study of 407 children with ADHD, MPH OROS was associated with a steady increase in mean absolute weight of 2.6 kg over 12 months.¹⁵⁸ Twenty-seven out of 568 (4.7%) children (mean age=8.7 years and 78% male) withdrew due to weight loss in a 24-month before-after study of mixed amphetamine salts (Adderall XR®).¹⁶⁶ Eligibility for this study was restricted to patients that completed either of two placebo-controlled trials without any clinically relevant adverse events or withdrew for any other reasons.¹⁶⁶

Based on 412 patients (children and adolescents) who had received atomoxetine for at least 2 years and had at least one post-baseline height and weight measurement, atomoxetine resulted in a mean decrease in expected weight of 0.87 kg, and decrease in expected height of 0.44 cm.¹⁴⁸ Analysis of change over time indicated that weight changes were greatest in the early months of treatment, with some regression toward the mean percentile at 2 years. Height changes appeared to occur over a longer period of time, but also regressed toward the mean by 2 years. Results from another before-after study of 10 boys (mean age NR) suggested that tomoxetine (same as atomoxetine) was associated with a weight loss of 1.15 kg after 10 weeks.¹⁶⁴

Tics

Four studies reported tic-related outcomes.^{150, 158, 160, 167} One of these is a long-term placebo-controlled trial¹⁶⁷ of MPH IR. Although the 1-year study started out with similar numbers assigned to placebo and MPH, but the study end 72 were on MPH and only 18 on placebo. Development of new tics or worsening of pre-existing tics was not different between the two groups. Two of the observational studies involved children^{150, 158} and the other involved adults.¹⁶⁰ These studies do not provide any information about how different pharmacologic treatments for ADHD compare in safety with regard to tic-related outcomes. Table 13 summarizes the characteristics and outcomes from these studies.

Table 13. Tic-related outcomes in observational studies

Study	Interventions (mean dose) Sample size	Population	Age Gender Duration	Tics
Children				
Law 1999	MPH 0.5 mg/kg twice daily vs Placebo N = 72	ADHD with no prior treatment for tics or ADHD	8.4 years 76% males 1 year	New onset tics: 19.6% MPH IR vs 16.7% placebo (NS) Exacerbation of pre-existing tics: 33% both groups (NS)
Gadow 1999	MPH 34.5 mg N=29	ADHD and chronic tics	8.8 years 91.2% male 2 years	Insignificant changes in frequency/severity of motor/vocal tics
Wilens 2003	MPH OROS 41 mg/day N=407	ADHD	9.2 years 83% male 1 year	New onset tics (% patients): 23 (6.4%)
Adults				
Horrigan 2000	Adderall – 10 mg/day, titrated (mean NR) N=24	ADHD	33 years 50% male 1 year	Motor tics (% patients): 1 (4%)

Seizures

The study that compared MPH (< 20 mg/day, 20.56 mg/day, and > 20 mg/day) to imipramine 65.4 mg/day and an untreated group (discussed earlier) also assessed seizures as an adverse event.¹⁵¹ None of the 70 males with hyperactivity experience a seizure over the one-year study period.

Cardiovascular adverse events

One study involved 169 children and adolescents that continued on open or blinded atomoxetine (max dose of 2 mg/kg divided into twice daily) for at least 1 year following 3 short-term, placebo-controlled trials.¹⁵³ The timing of ECG measurements is not stated, but is presented by increasing dose. Linear regression suggests that there is no evidence of an increase in QTc with increasing dosage of atomoxetine.¹⁵³

Substance Abuse

Two studies assessing the risk of substance abuse among children treated with MPH or not treated, with similar duration of follow-up (mean just under 2 years) found no differences between the groups in the risk of using cigarettes, marijuana, or alcohol.^{168, 169} A questionnaire – based survey reported small numbers of teenagers who reported having taken higher than prescribed doses, purposefully mixing ADHD drugs with other substances, having lost a bottle of ADHD medications, etc.¹⁷⁰ Multiple ADHD medications had been used by the survey respondents, and these results do not provide insight into comparative risk for future substance abuse among users of ADHD drugs.

Injuries

A retrospective database study analyzed an association between childhood behavioral disorders and common childhood injuries by using the British Columbia Linked Health Data Set to identify injuries. Children with behavioral disorders were identified using MPH prescriptions as a proxy for diagnosis using data in a Triplicate Prescription Program.¹⁴⁹ Injury frequencies in

children prescribed MPH at least once between 1/1/1990 and 12/31/1996 (n=16,806) were compared to those in children not taking MPH (n=1,010,067). Children were 51.4% male and aged less than 19 years. Mean duration of exposure was not identified. Odds of any injury (fractures, open wounds, poisoning/toxic effect, intracranial, concussion, and burns) were significantly higher in children taking MPH than for those not taking MPH (OR 1.67, 95% CI 1.54 to 1.81), even after adjusting for baseline age, sex, socioeconomic status and region. This study design clearly suffers from lack of sensitivity to diagnosis, in that an unknown number of children with behavioral disorders are included in the group not taking MPH. Since MPH was used simply as a proxy for behavioral disorders, the relationship between the drug and the increase in injuries is not necessarily clear.

Suicide

One before-after study followed 8 adult males (mean age of 27.2 years) that continued on open MPH for three to six months subsequent to participation in short-term clinical trials.¹³¹ One participant (12.5%) attempted to commit suicide by consuming a month's supply of MPH.

Post-marketing safety concerns

The information provided below does not come from comparative studies but is included here to provide a complete and current picture of important safety concerns.

An analysis conducted by the Office of Drug Safety (ODS) in April 2004 evaluated reports of sudden death or serious cardiovascular events associated with use of amphetamine and methylphenidate products at usual dosages (http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4202B1_05_FDA-Tab05.pdf) received by the FDA Adverse Event Reporting System (AERS). ODS recently updated this analysis to include a broader reporting period and which also included atomoxetine (http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4210b_06_01_Gelperin.pdf). The results of these 2 analyses are summarized below.

Table 14. Cardiovascular risk of ADHD drugs

	Amphetamine products		Methylphenidate products		Atomoxetine	
January 1, 1999 through December 31, 2003						
Children	Cases	Per Million Rx's	Cases	Per Million Rx's		
Sudden Death	12	0.36	7	0.16		
Serious CV Events	18	0.53	8	0.18		
Adults						
Sudden Death	5	0.53	1	0.07		
Serious CV Events	17	1.79	11	0.74		
January 1992 through February 2005						
Children	Cases	Per 100,000 Patient-Years	Cases	Per 100,000 Patient-Years	Cases	Per 100,000 Patient-Years
Sudden Death	13	0.3	11	0.2	3	0.50
Adults						
Sudden Death	6	0.3	2	0.1	4	2.8

The more recent findings were presented in meetings on February 9, 2006 for the Drug Safety and Risk Management Advisory Committee (DSaRM) and on March 22, 2006 for the Pediatric Advisory Committee. These committee meetings were convened to discuss (1) how to design future studies to further investigate and characterize the potential cardiovascular risks

associated with stimulant and/or atomoxetine treatment for ADHD; and (2) how to convey information about potential cardiovascular risks of stimulants and/or atomoxetine to physicians and parents (e.g., labeling changes, other mechanisms). In both meetings there was consensus that it is not yet possible to determine causality, impact of pre-existing heart disease, and magnitude of risk due to limitations in the reliability of spontaneous report data. Reports indicate that the DSaRM called for adding a black box warning to ADHD drug product labels. The Pediatric Advisory Committee agreed there was a need to supplement the labels with information about potential cardiovascular risks, but concluded that the available evidence does not yet warrant the seriousness level of a black box warning. Other potential risks discussed by the committees included suicidality, aggression and/or violent behavior and psychosis and/or mania symptoms. To date, no action on these recommendations by the FDA has been made public.

Amphetamine Mixture SR (Adderall XR®). Health Canada suspended the market authorization of ADDERALL XR® in February 2005. Health Canada's decision was a result of 20 international reports of sudden death in patients taking either Adderall or Adderall XR (Adderall IR was not marketed in Canada). FDA review of the reports of sudden deaths in children resulted in the following statement: "SUD (sudden unexplained death) has been associated with amphetamine abuse and reported in children with underlying cardiac abnormalities taking recommended doses of amphetamines, including Adderall and Adderall XR. In addition, a very small number of cases of SUD have been reported in children without structural cardiac abnormalities taking Adderall. At this time, FDA cannot conclude that recommended doses of Adderall can cause SUD, but is continuing to carefully evaluate these data." (<http://www.fda.gov/cder/drug/infopage/adderall/default.htm>).

In August of 2005, following a recommendation by the New Drug Committee (NDC), Health Canada reinstated the licensure of Adderall XR®, with modifications to the drug label, including: warnings that sudden death has occurred at therapeutic doses in children with structural cardiac abnormalities and that Adderall XR should generally not be used in patients with pre-existing structural cardiac abnormalities. (http://www.hc-sc.gc.ca/ahc-asc/media/nr-cp/2005/2005_92_e.html)

In February 2006, the FDA convened a committee to review the data on Adderall XR. To date, no recommendations or conclusions have been published.

Atomoxetine. Two case reports (via the FDA MedWatch system) of hepatotoxicity in patients taking atomoxetine (one adult, one child) have resulted in the addition of a warning in the product labeling: "Postmarketing reports indicate that STRATTERA can cause severe liver injury in rare cases. Although no evidence of liver injury was detected in clinical trials of about 6000 patients, there have been two reported cases of markedly elevated hepatic enzymes and bilirubin, in the absence of other obvious explanatory factors, out of more than 2 million patients during the first two years of postmarketing experience. In one patient, liver injury, manifested by elevated hepatic enzymes (up to 40 X upper limit of normal (ULN)) and jaundice (bilirubin up to 12 X ULN), recurred upon rechallenge, and was followed by recovery upon drug discontinuation providing evidence that STRATTERA caused the liver injury. Such reactions may occur several months after therapy is started, but laboratory abnormalities may continue to worsen for several weeks after drug is stopped. Because of probable underreporting, it is impossible to provide an accurate estimate of the true incidence of these events. The patients described above recovered from their liver injury, and did not require a liver transplant. However, in a small percentage of

patients, severe drug-related liver injury may progress to acute liver failure resulting in death or the need for a liver transplant. STRATTERA should be discontinued in patients with jaundice or laboratory evidence of liver injury, and should not be restarted. Laboratory testing to determine liver enzyme levels should be done upon the first symptom or sign of liver dysfunction (e.g., pruritus, dark urine, jaundice, right upper quadrant tenderness, or unexplained “flu-like” symptoms).¹¹²

In September 2005, FDA issued a public health advisory and a directive to update the product label with a black boxed warning regarding a potential association of atomoxetine and risk of suicidality in children and adolescents.¹⁷¹ (<http://www.fda.gov/bbs/topics/news/2005/new01237.html>) This came after FDA review of results from an unpublished meta-analysis of 12 placebo-controlled trials of children in which atomoxetine was associated with significantly higher risk of suicidal ideation than placebo: 0.37% (5/1357) vs 0% (0/851); Maentel-Haenzel Incidence Difference 0.46, 95% CI 0.09, 0.83; $p=0.016$. Suicide attempts were slightly higher with atomoxetine; 0.07% (1/1357) vs 0% (0/851).¹⁷¹

Other. A recent study by El-Zein et al¹⁷², with outcomes outside the scope of this review, has raised the question of MPH’s potential cytogenetic effects. This has prompted multiple studies to assess MPH’s clastogenic potential. Results of these studies relevant to this review will be included in future updates as they become available.

Key Question 3: Subgroups.

Are there subgroups of patients based on demographics (age, racial groups, gender, ethnicity), other medications, or co-morbidities for which one pharmacologic treatment is more effective or associated with fewer adverse events?

ADHD subtypes, comorbidities, and race or ethnicity were not recorded in most randomized controlled trials and observational studies. For example, only one-quarter of all studies of school-aged children reported ADHD subtype prevalence rates. Importantly, of those that did record demographic information, only one poor quality trial reported results of a subgroup analysis of Black children with ADHD.¹⁷³ While the data available from the studies that do report this information can be useful in determining the generalizability of results, the lack of attention to assessing the impact of these factors means there is almost no evidence on potential differences in response or adverse events.

Race or Ethnicity

Only one-half of all studies of elementary school-aged children reported race or ethnicity among the baseline characteristics. Study populations were made up primarily of White participants, with a few exceptions. The scales used in the trials included may not perform well in all ethnic groups, or when translated into languages other than English. Since the majority of trials were performed in English speaking populations, with primarily white participants, these issues were not explored in the studies.

A subgroup analysis conducted specifically to evaluate the comparative efficacy and safety of *open-label* methylphenidate OROS and atomoxetine in 183 Black children with ADHD (out of 1,323 children that participated in the overall trial) found treatment outcomes to be similar to those for the overall study population.¹⁷³ Main findings from the subgroup analysis are summarized in Evidence Table 3, but will not be discussed in detail here due to concerns about study quality. This trial (the FOCUS trial) was rated poor quality based on a combination of flaws including undescribed methods of randomization and allocation concealment, significant between-groups baseline differences in ADHD severity, and lack of information about attrition and number of patients included in analyses (Evidence Table 4).

MPH IR.

MPH IR 0.15, 0.30 and 0.50 mg/kg was studied in a placebo-controlled, crossover trial (2 weeks in each arm) of 11 Black male adolescents (mean age=13.6 years).^{103, 147} MPH IR had a positive effect on 75% of efficacy measures. This response rate is similar to that seen in other placebo-controlled trials of MPH IR. MPH IR was associated with significant linear elevations diastolic blood pressure among these patients.

An analysis of California Medicaid claims data suggests that mean persistence (days of treatment without any 30-day gaps) was longer for children taking MPH ER formulations (OROS and SODAS) than for those taking MPH IR regardless of ethnicity (White, Black, Hispanic)⁴¹. This same data indicates that mean treatment durations overall (MPH OROS, SODAS, and IR) were significantly shorter for children of Black (survival time ratio (STR) 0.77; 95% CI 0.73-0.80), Hispanic (STR 0.81; 95% CI 0.78-0.84) and other ethnicities (STR 0.81; 95% CI 0.75-0.87) than for White children.

Gender

Girls typically make up only a small proportion of the total children enrolled in ADHD trials, which reflects the differential in the rates of ADHD diagnoses among the sexes.

In a study designed to assess differences in response between hyperactive boys and girls, 20 girls and 20 boys, mean age 6 years were enrolled in a randomized crossover study of placebo, MPH IR 0.15 mg/kg/day and 0.35 mg/kg/day each given for 7 to 10 days.¹⁷⁴ Outcomes assessed were based on mother-child interactions (e.g., mother gives command, does child comply?). At baseline, there were some differences between boys and girls. The mothers of boys gave more directives during free play to boys, and during the task period, boys were less compliant with their mothers' commands. Overall, there were no drug effects on measures during free play in any group/drug dose combination. The comparison of effects between the sexes revealed that during the task period, boys were significantly more compliant and mothers gave fewer commands and more praise comments than in the girls group. Considering the differences at baseline, this could be interpreted to indicate that the MPH IR was more effective in boys than girls in improving mother-child interactions. However, the authors do not interpret the data this way, but rather that mothers respond differently to improvements in behavior in boys than girls. These outcome measures are not used in other studies, however, and relating these findings to other studies is not possible.

A second study designed to assess differences between the response in boys and girls when taking MPH IR enrolled 24 children.¹⁷⁵ Children were randomly assigned to placebo or MPH IR, and then crossed over to the other treatment. The randomization was done daily, with 5 to 9 days of data recorded for each condition. A number of outcome measures were used. The MANOVA analysis of results indicated a significant effect of MPH IR, but found no interaction between drug and gender.

In a study of 42 girls,⁴⁵ analyses were primarily conducted combining data for MPH IR and DEX IR and making an *indirect* comparison to a study of boys conducted by the same group of researchers earlier.⁷⁵ This report concludes that there are no striking differences between boys and girls in response to these 2 stimulants, and that both can be effective in either group.

Data from girls enrolled in 2 separate placebo-controlled trials of atomoxetine with identical protocols were analyzed post-hoc to assess the effects in this subgroup of children.¹⁷⁶ These placebo-controlled trials are reported in full above. This analysis of 52 girls reported similar efficacy to that reported for the whole trial group (atomoxetine superior to placebo on most measures) but did not make a comparison of the effects in boys versus girls.

Extremely limited adverse event data was provided in these studies, and no comparison between boys and girls can be made on these measures.

ADHD Subtypes

Only two trials were identified that reported results of subgroup analyses based on ADHD diagnostic subtypes and both involved comparisons of atomoxetine to placebo in school-aged children.^{94, 100} Results from both trials suggest that atomoxetine was associated with superior efficacy relative to placebo in all subgroups of children regardless of diagnostic subtypes.

Co-morbidity

Rates of comorbidities were reported in 48% of all studies. With the exception of depression, the ranges of comorbidities reported in these trials encompass the American

Academy of Pediatrics estimates on prevalence of common comorbidities: Oppositional defiant disorder=35.2 (27.2, 43.8), conduct disorder=25.7 (12.8, 41.3), anxiety disorder=25.8 (17.6, 35.3) and depressive disorder=18.2(11.1, 26.6).⁵⁶ One placebo-controlled trial of atomoxetine¹³⁶ in adults reported results of subgroup analyses stratified by comorbidities. Atomoxetine treatment effects were not altered by the presence or absence of “psychiatric comorbidity” in a 3-week trial of 22 adults.¹³⁶ This trial does not provide evidence of comparative efficacy among subgroups of patients with comorbidities.

Tic disorders including Tourette’s Disorder

A concern over stimulant drugs increasing or worsening tic disorders has resulted in several trials enrolling children comorbid with ADHD and a tic disorder. Two placebo controlled trials enrolled children with tic disorders.^{177, 178} Based on these studies, it appears that there is no significant effect of MPH IR compared to placebo with respect to severity of tics (Table 15). These studies also found MPH IR to have a positive effect on ADHD symptoms, compared to placebo.

Table 15. Tic Severity Ratings in trials of drugs to treat ADHD

Study	Design/Dose	YGTSS		
Placebo Controlled Studies		Drug	Placebo	
Sverd 1992	MPH IR	Global Severity score: 37.4	0.1 mg/kg/day: 33.0	ANOVA NS
	Placebo		0.3 mg/kg/day: 38.4 0.5 mg/kg/day: 35.5	
Gadow 1995	MPH IR Placebo	Data NR	Data NR	ANOVA group x dose NS

Mental Retardation

Seven randomized crossover trials of MPH IR versus placebo in children with mental retardation and ADHD (five conducted by the same group of researchers) were found.¹⁷⁹⁻¹⁸⁵ The trials were small, ranging in size from 11 to 44 children. One assessed only adverse events,¹⁸⁰ and another enrolled preschool children.¹⁸⁴ Most enrolled predominantly white children, with one exception.¹⁸⁶ All participants in the Agarwal 2001 study were Indian.¹⁸⁶ All children enrolled had mild to borderline mental retardation, as described by the eligibility criteria in each study. All of these studies had a 7 day treatment phase, and assigned patients to 0.3 and 0.6 mg/kg doses given twice daily. One crossover trial also included exposure to a low-dosage of 0.15 mg/kg.¹⁸⁵ Tables 16 and 17 summarize the findings of these studies.

Table 16. Main Outcomes in Studies in Children with ADHD and Mental Retardation

Study	N Age IQ*	Main Outcomes
MPH IR		
Pearson 1993	24 10.9 yrs 56.5	Teacher behavioral ratings (ACTeRS, CTRS): significant improvement demonstrated on 9 of 11 (81.8%) subscales for high-dose and 3 of 11 (27.3%) for medium dose; low-dose was similar to placebo on all subscales Parent behavioral ratings (CPRS, ABC, RBPC, PIC-R): only instance of superiority of any dose of MPH IR relative to placebo among the 19 subscales was for the high-dose on the impulsive-hyperactive index of the CPRS
Handen 1990	12 NR 65	6 of 8 (75%) of items assessed during the week by the children's teachers and 14 of 21 (67%) of items assessed during laboratory sessions showed one or both MPH IR doses superior to placebo. Teachers did not find any effect on the numbers of independent tasks completed or % correct with either dose. While teachers found both doses superior to placebo, the laboratory assessments indicated the 0.6 mg/kg dose to be superior to placebo on more measures.
Handen 1992	14 9 yrs 65	6 of 9 (67%) items assessed during the week by the children's teachers and 13 of 38 (34%) of items assessed during laboratory sessions showed one or both MPH IR doses superior to placebo. Teachers rated 0.6 mg/kg better than placebo on more measures, but did not find any effect on the numbers of independent tasks completed or % correct with either dose. Conversely, the laboratory assessments indicated the 0.3 mg/kg doses to be superior to placebo on more measures. 64% classified as responders to MPH (dose groups combined, defined as 40% decrease in CTRS hyperactivity).
Handen 1995	22 9 yrs 64	This study only assessed free play and a "restricted academic task" (toys in a room and the adult leaves the room but the child is told not to touch the toys). 60% of each of the dependent measures showed MPH IR superior to placebo with the 0.6 mg/kg dose better on more measures than the 0.3 mg/kg dose.
Handen 1996	44 9 yrs 64	Overall, 66% were classified as responders (dose groups combined, defined as 50% decrease in CTRS hyperactivity). However, of these 29 children, 13 were responders only in the laboratory classroom, and 7 only in the weekday classroom. 9 (20%) were responders in both. All 5 measures by teachers and 5 behavior measures assessed in the laboratory classroom found MPH superior to placebo. Only the Selective Reminding Test (short-term auditory learning) showed no drug effect.
MPH IR		
Preschool Children		
Handen 1999	11 5 yrs 60	5 of 34 measures indicated 0.6 mg/kg MPH IR superior to placebo: CTRS hyperactivity, inattention-passivity, hyperactivity index; Preschool Behavior Questionnaire: hyperactive-distractible, and Play Session: intensity. No measures significantly better than placebo with 0.3 mg/kg/day. 73% classified as responders to MPH IR (dose groups combined, defined as 40% decrease in CTRS hyperactivity or PBQ hyperactive-distractible scores).

*Mean, as assessed by the Wechsler Intelligence Scale for Children – Revised; ACTeRS=ADD-H Comprehensive Teacher Rating Scale; CTRS=Conners Teacher Rating Scale; CPRS=Conners Parent Rating Scale; ABC=Aberrant Behavior Checklist; RBPC=Revised Behavioral Problem Checklist; PIC-R=Personality Inventory for Children-Revised

Table 17. Adverse Events in Studies in Children with ADHD and Mental Retardation

Study	Adverse Events
MPH IR	
Handen 1990	Increased staring with MPH IR in 50%, increased drowsiness in 42%. Severe social withdrawal seen at 0.3 mg/kg doses in 1 patient.
Handen 1992	Not reported
Handen 1995	Not reported
Handen 1996	Not reported
Handen 1991 Adverse Events only	3 of 13 adverse events assessed indicated MPH IR caused fewer reports than placebo (both doses caused significantly less “high activity”, and the 0.6 mg/kg dose caused fewer episodes of irritability and anxiety.) The intensity of adverse events was assessed in 14 children, 5 of 10 adverse events assessed showed lower intensity with MPH IR than placebo (staring, irritability, anxiety, moody, and high activity).
Preschool Children	
Handen 1999	5/11 had “significant adverse effects”. Social withdrawal in 6/11; severe in 4 – with the higher dose.

Taken together, these studies indicate that MPH IR is effective in improving some measures of ADHD symptoms. Adverse events were common, with increased staring and social withdrawal being prominent with MPH IR. Unfortunately, these do not provide comparative evidence with other drugs.

Autism

A very small (n = 13) randomized crossover trial of placebo and 2 doses of MPH IR enrolled 13 children with ADHD and autism or pervasive developmental disorder (PDD) (mean age 7 years). The children’s cognitive function ranged from severely mentally retarded (23%) to normal (average IQ, 8%). Two children (15%) did not have a diagnosis of ADHD, but oppositional defiant disorder only. Overall, 54% were comorbid with oppositional defiant disorder. Additionally, one child (each) had Mosaic Downs Syndrome, Sleep-wake schedule disorder, anxiety disorder, and mixed seizure disorder and 31% had a diagnosis of PDD Not Otherwise Specified rather than autism. This study is unique in that it enrolled a higher than average proportion of black (54%) and Hispanic (15%) children. Seven children were outpatients enrolled in special education programs while 6 were inpatients or in intensive day-treatment programs. The children were randomized to MPH IR 0.3 mg/kg./day, 0.6 mg/kg./day or placebo, with the lower dose of MPH IR always preceding the higher dose. Dosing could be divided into 2 or 3 daily doses, at the choice of parents. Outcome measures assessed by teachers or program staff at the end of a 7-day dosing period included the Conners Teacher Scale Hyperactivity Index, the IOWA CTRS, the Aberrant Behavior Checklist (ABC), and the Child Autism Rating Scale (CARS). Sixty-two percent were classified as responders to MPH IR (any dose, response = 50% reduction on the Conners Teachers Scale Hyperactivity Index). Based on final score at 7 days, both MPH doses were superior to placebo on the Conners and IOWA scales, but on the ABC scale, the 0.6 mg/kg/day dose was superior to placebo on hyperactivity ratings, and both were superior on the inappropriate speech ratings. The other 3 items did not indicate a difference from placebo for MPH IR. No difference from placebo was found the autism rating scale (CARS). An analysis of age and IQ did not reveal differences in response rates based on these factors. Eleven adverse events were reported across the three medication conditions, with “sad/unhappy/depressed” increasing with increasing doses of MPH IR and drowsy/dull remaining consistent across the MPH IR treatments. The other reported adverse events decreased across treatment conditions in order assigned (the effect was considered transient).

Epilepsy

A small (n= 30) randomized crossover study of children (mean age 10 years) with ADHD and epilepsy studied the effect of adding placebo or MPH IR to the child's current anti-epilepsy regimen.¹⁸⁷ The study design was unusual; children were followed for 2 months as a baseline period, then given MPH IR (open-label, uncontrolled) for 2 months however, on 2 days (one at the end of the baseline period, and one at the end of the MPH IR open label period). On these days, half of the children were given a single dose of MPH IR, and the other half placebo (non-random assignment). Outcome measures for these two days were antiepileptic drug serum levels, encephalography, and the continuous performance test (CPT). Of these, only the CPT meets criteria for this review. MPH IR was shown superior to placebo on the CPT based on speed of response and more "time on task" during the 45-minute test. The data presented on adverse events relates primarily to an observational period, although is not presented clearly. Loss of appetite was reported as an adverse event related to MPH IR that was not persistent. All others were assessed as being transient.

Substance Abuse Disorders

One placebo-controlled trials of MPH in **adult** patients with ADHD and current cocaine dependence does not provide comparative evidence.¹²⁸ This placebo-controlled, 13-week, parallel-group trial of MPH IR reported results for 48 patients with ADHD (DSM-IV) and current cocaine dependence. Outcomes were measured using the ADHD Symptom Checklist, Global Improvement Scale (GIS), and Beck Depression Inventory. Mean participant and physician ratings at the last visit on the 7-point GIS were significantly greater in the MPH group compared to the placebo group. MPH and placebo had similar effects on ADHD symptom outcomes. Rates of adverse events were similar for MPH and placebo, with one exception. A significantly greater proportion of patients experienced insomnia or trouble sleeping while taking MPH than placebo (63% vs 33%, $p<0.05$).

Oppositional Defiant Disorder

Outcomes from a subset of children with coexisting ADHD and oppositional defiant disorder (ODD) were pooled across two placebo-controlled trials of atomoxetine.¹⁰¹ Atomoxetine was associated with significantly greater reductions in ADHD-RS Total Scores than placebo (-17.0 vs -7.5; $p<0.001$) in 98 of the original 291 patients⁹⁴ with co-existing ADHD and ODD after 9 weeks.¹⁰¹

Bipolar Disorder

When added to divalproex, amphetamine mixture(Adderall®) was associated with significantly greater improvements in ADHD symptoms than placebo after 4 weeks, but had no effect on bipolar disorder symptoms in 30 pediatric patients with comorbid ADHD and bipolar disorder (mean age 9.8 years).¹⁸⁸ This fair-quality study included 30 children who achieved a significant response to 8 weeks of open-label divalproex, out of 40 enrolled in the run-in phase.

Limitations of this Review

As with other types of research, it is important to recognize the limitations of this systematic review. These can be divided into those relating to generalizability of the results and those relating to methodology within the scope of this review. The generalizability of the results is limited by the scope of the key questions and inclusion criteria, and the generalizability of the studies included. The great majority of studies included narrowly or poorly defined patient populations who met strict criteria for case definition, had few comorbidities, and used few or no concomitant medications. One concern about this group of studies is the variation in diagnostic criteria, particularly comparing studies conducted recently to those conducted in previous decades. Another concern is the handling of subtypes of ADHD in these studies. While many studies identify the proportions of patients diagnosed with various subtypes, stratification or analysis of the results based on these is lacking. Similarly, common co-morbid conditions are not well addressed by the studies. In large part, the failure to address either subtypes or co-morbidities may be due to small sample sizes involved in most studies, but these are serious short-comings that should not be ignored. The failure of these studies to assess the effect of prior medication exposure or concurrent treatment with other psychoactive medications on outcomes is another serious issue, particularly when comparing older studies where very few patients had prior exposure to newer studies where large proportions did have exposure. Minorities and the most seriously ill patients were underrepresented.

Methodological limitations of the review within the defined scope include the exclusion of studies published in languages other than English, and the lack of a specific search for unpublished studies.

OVERALL SUMMARY

Table 18. Overall Table Summary

Key Question 1: Benefits	Quality of Evidence	Conclusion
General		
Effectiveness	Poor, no trials found	No conclusions about comparative effectiveness of different pharmacotherapies for ADHD can be made
Young children		
Efficacy	Overall: Poor	
	MPH IR	MPH IR was superior to placebo on CPRS-R efficacy outcomes
Children		
Efficacy	Overall: Fair (individual ratings below)	
Stimulants		
IR vs SR formulations	MPH IR vs MPH SR (fair)	Studies of MPH IR versus extended release formulations in children did not show an overall difference in efficacy.
SR vs SR formulations	MPH SR vs MPH SR formulations (poor)	Very limited evidence suggests that Ritalin LA® was superior to Concerta® on some, but not all efficacy outcomes. Limited evidence suggests that Metadate CD® was superior to Concerta® on outcomes in the morning; they had similar effects in the afternoon; and Concerta® was superior in the evening.
IR vs IR	DEX vs MPH IR (good)	The body of evidence clearly indicates no difference in efficacy between DEX and MPH IR.
	Amphetamine mixture vs MPH IR (fair)	Amphetamine mixture was superior to MPH IR on a few efficacy outcome measures in two trials, but clear evidence of superiority is lacking.
	DEX IR vs DEX ER vs Amphetamine mixture (poor)	Evidence on the comparison of DEX IR versus SR versus Amphetamine mixture may suggest that measures made in the morning show DEX IR superior to DEX SR, and afternoon measures show DEX SR superior to Amphetamine mixture.
	Modafinil (poor)	Very limited evidence from placebo-controlled trials suggests modafinil is superior to placebo on most efficacy measures.
	Dexmethylphenidate (NA)	Only incomplete evidence was found.
Atomoxetine		
	Poor	
	Atomoxetine vs MPH IR	Limited evidence suggests a lack of a difference in efficacy compared to MPH IR
	Atomoxetine vs amphetamine mixture XR	Limited evidence suggests that amphetamine mixture SR is superior to atomoxetine on most efficacy measures
Adolescents		
Efficacy	Poor	
	MPH IR vs MPH OROS	Functional capacity: NR Short-term improvements of core ADHD symptoms: NR Driving performance: MPH OROS > MPH IR in evening and at night

	Placebo-controlled studies of MPH IR	Functional capacity: NR Short-term improvements of core ADHD symptoms: MPH IR generally efficacious
Adults		
Stimulants	Fair	
short-term trials	DEX IR vs MPH IR	One HTH trial suggests no differences in symptom improvement Indirect comparisons from placebo-controlled trials do not suggest clear differences in response rates for DEX IR (1 trial) and MPH IR (4 trials)
	Adderall vs Placebo	Limited indirect comparisons from placebo-controlled trials suggests that response rates are similar to other stimulants
longer-term observational study	MPH IR vs untreated historical controls	MPH IR group had lower rates of current psychiatric care than the untreated group in a 10-12 year follow-up study of males diagnosed with hyperactivity in childhood. Other outcomes were mixed.
Atomoxetine	Poor	
	Atomoxetine vs Placebo	Limited indirect comparisons from placebo-controlled trials suggests that response rates are similar to stimulants. Mixed effects on quality of life compared to placebo.

Key Question 2: Safety	Quality of Evidence	Conclusion
Short-term Trial Evidence		
Young children	Poor – 1 placebo-controlled trial of MPH	Indirect comparisons cannot be made; MPH associated with higher rates of adverse events than placebo
Children	Poor	Very few studies reported methods for assessing adverse events a priori
	MPH IR vs MPH SR	There is no evidence of a difference in adverse events between IR and SR formulations.
	MPH SR vs MPH SR formulations	No differences in adverse events were found.
	DEX vs MPH IR	Limited evidence from short-term trials suggests that weight loss is greater with DEX than MPH IR
	Amphetamine mixture vs MPH IR	Very limited evidence suggests that twice daily dosing of Amphetamine mixture led to higher rates of loss of appetite and sleep trouble.
	DEX IR vs DEX ER vs Amphetamine mixture	Transient weight loss was greater with Amphetamine mixture and DEX SR than with DEX IR.
	Comparisons to atomoxetine	Atomoxetine caused more vomiting and somnolence than MPH IR and amphetamine mixture XR. MPH IR caused more 'abnormal thinking'. Amphetamine mixture XR caused more insomnia.
Adolescents	Poor	Very few studies reported methods for assessing adverse events a priori
	Placebo-controlled studies of MPH IR	No indirect comparisons possible. Placebo-controlled trials only involved assessment of MPH IR.
Adults	Poor	Very few studies reported methods for assessing adverse events a priori
Stimulants	Adderall and MPH IR	Indirect comparisons from placebo-controlled trials suggest both are associated with higher rates of insomnia, appetite loss and withdrawal due to adverse events than placebo
	DEX IR and MPH SR	Indirect comparisons cannot be made.
Atomoxetine	Atomoxetine	Very limited indirect comparative evidence across few placebo-controlled trials suggests that atomoxetine is associated with rates of insomnia, appetite loss and withdrawals due to adverse events similar to stimulants

Long-Term Safety – Observational Studies		
Mixed populations, primarily children	Fair	
	Height	<ul style="list-style-type: none"> • DEX vs MPH IR: Mixed findings. DEX=MPH in 6-year height increases in one study; DEX>MPH in 2-year height decreases in the other • MPH IR vs unmedicated controls: No significant differences in two studies • MPH IR in uncontrolled studies: Inconsistent effects across four studies • Atomoxetine: Uncontrolled studies suggest that height changes are similar to those reported with MPH IR, and are also transient
	Weight	<ul style="list-style-type: none"> • DEX vs MPH: Three studies consistently suggest that DEX>MPH in weight gain suppression in the first 1-2 years. The longest-term (5 years) of these studies also reported that DEX=MPH in exceeding weight gain expectations at final follow-up. These findings are weakened by methodological flaws, however. • MPH IR in other comparative (imipramine and unmedicated hyperactives or healthy controls) and noncomparative studies: Evidence does not support an indisputable relationship between MPH and weight gain suppression • MPH OROS and tomoxetine (atomoxetine): Evidence from noncomparative studies (one each) doesn't suggest weight gain suppression effects • Atomoxetine: Uncontrolled studies suggest that weight changes are similar to those reported with MPH IR, and are also transient.
	Tics, seizures, cardiovascular adverse events, injuries, and attempted suicide	No comparative evidence
	Drugs with warnings or removal from market	<p>Adderall XR®: reports of sudden death in children - withdrawn from market in Canada, not US</p> <p>Atomoxetine: reports of hepatotoxicity led to additional warnings in product label</p>

Key Question 3: Subgroups	Quality of Evidence	Conclusion
Children	Fair	
	ADHD Subtypes or Severity	Only ¼ of studies reported prevalence of the ADHD subtypes, and none analyzed data based on these. Lack of consistency in measurement and reporting of severity prohibits analysis.
	Race / Ethnicity	Most trials conducted in primarily white populations. Ethnicity/race only reported in 1/2 of studies. No analyses based on race. Very limited evidence suggests MPH IR n African American boys results in response rates similar to other populations studied.
	Age	Evidence in adolescents is very limited. The mean age of children in the trials is 8 to 10 years.
	Gender	No difference in efficacy can be found between boys and girls.
	Common Co-morbidities	Rates on commonly occurring comorbidities reported in only ½ of trials. No study analyzed data stratified by these conditions. Rates of prevalence of these among study participants were generally similar to prevalence rates reported by AAP for the overall ADHD population.
	Tic Disorders	No consistent evidence that MPH IR increased tic severity or frequency compared to placebo. All of these studies of MPH IR showed a benefit of MPH IR on ADHD outcome measures compared to placebo.
	Mental Retardation	MPH IR is beneficial on most ADHD outcomes compared to placebo. Adverse events include staring and social withdrawal. Adverse events include drowsiness and blood pressure lowering.
	Autism	Very limited evidence suggests that MPH IR is beneficial on most ADHD outcomes compared to placebo.
	Epilepsy	Very limited evidence suggests that MPH IR is beneficial on most ADHD outcomes compared to placebo.
	Oppositional defiant disorder	Very limited evidence suggests that atomoxetine is beneficial on most ADHD outcomes compared to placebo
	Bipolar Disorder	Very limited evidence suggests that mixed amphetamine salts (Adderall®) is benefit on most ADHD outcomes compared to placebo
Adults	Poor	
	Age groups, gender, racial/ethnic groups, or comorbidities	Very limited evidence suggests that MPH IR response rates were not affected by co-existing cocaine dependence in a placebo-controlled trial of adults. Very limited evidence suggests that presence or absence of “psychiatric illness” did not alter treatment effects of atomoxetine compared to placebo. No conclusions about comparative efficacy or safety in subgroups of adults can be made.

REFERENCES

1. NIH. NIH Consensus Statement: Diagnosis and treatment of attention deficit hyperactivity disorder. Accessed 2, 16.
2. Helmerichs R. *Historical Definitions and Nomenclatures of the Label 'ADHD': An Investigating into Attention-deficit and Hyperactive Behavior through Time*. Menomonie: The Graduate School, University of Wisconsin-Stout; 2002.
3. Goldman LS, Genel M, Bezman RJ, Slanetz PJ. Diagnosis and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Council on Scientific Affairs, American Medical Association. *Journal of the American Medical Association*. 1998;279(14):1100-1107.
4. Anonymous. *Diagnostic and statistical manual of mental disorders : DSM-IV*. 4th ed. Washington, DC: American Psychiatric Association; 1994.
5. Jadad AR, Boyle M, Cunningham C, Kim M, Schachar R. Treatment of attention-deficit/hyperactivity disorder. *Evidence Report: Technology Assessment (Summary)*. 1999(11):i-viii, 1-341.
6. Dunne JE, Arnold V, Benson S, et al. Summary of the practice parameters for the assessment and treatment of children, adolescents, and adults with ADHD. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1997;36(9):1311-1318.
7. Kessler RC, Adler L, Barkley RA, et al. The prevalence and correlates of adult ADHD in the United States: results from the national comorbidity survey replication. *American Journal of Psychiatry*. 2006;163:716-723.
8. Green M, Wong M, Atkins D, Taylor J, Feinleib M. Diagnosis of Attention-Deficit/Hyperactivity Disorder (Technical Review #3). *Rockville, MD: Agency for Health Care Policy and Research*. 1999.
9. Buros OK, (Eds). *The Ninth Mental Measurements Yearbook*. Lincoln, NE: Buros Institute of Mental Measurements; 1985 v2.
10. Conoley JC, Kramer JJ, (Eds). *The Tenth Mental Measurements Yearbook*. Lincoln, NE: Buros Institute of Mental Measurements; 1989.
11. Conoley JC, Impara JC, (Eds). *The Twelfth Mental Measurements Yearbook*. Lincoln, NE: Buros Institute of Mental Measurements; 1995.
12. Impara JC, Plake BS, (Eds). *The Thirteenth Mental Measurements Yearbook*. Lincoln, NE: The University of Nebraska-Lincoln.; 1998.
13. Kramer JJ, Conoley JC, (Eds.). *The Eleventh Mental Measurements Yearbook*. Lincoln, NE: Buros Institute of Mental Measurements; 1992.
14. Mitchell JV, (Ed). *The Ninth Mental Measurements Yearbook*. Lincoln, NE: Buros Institute of Mental Measurements; 1985 v1.
15. Plake BS, Impara JC, (Eds). *The Fourteenth Mental Measurements Yearbook*. Lincoln, NE: The University of Nebraska-Lincoln.; 2001.
16. Plake BS, Impara JC, Spies RA, (Eds.). *The Fifteenth Mental Measurements Yearbook*. Lincoln, NE: Buros Institute of Mental Measurements; 2003.
17. Kunz R, Oxman AD. The unpredictability paradox: review of empirical comparisons of randomised and non-randomised clinical trials. *BMJ*. 1998;317:1185-1190.
18. Pocock SJ, Elbourne DR. Randomized trials or observational tribulations? *New England Journal of Medicine*. 2000;342(25):1907-1909.
19. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med*. Jun 22 2000;342(25):1887-1892.
20. Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials.[comment]. *New England Journal of Medicine*. 2000;342(25):1878-1886.
21. Harris RP, Helfand M, Woolf SH, et al. Current methods of the third U.S. Preventive Services Task Force. *American Journal of Preventive Medicine*. 2001;20(3S):21-35.

22. Anonymous. *Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews CRD Report Number 4 (2nd edition)*. York, UK: NHS Centre for Reviews and Dissemination; 2001. 4 (2nd edition).
23. Klassen A, Miller A, Raina P, Lee SK, Olsen L. Attention-deficit hyperactivity disorder in children and youth: A quantitative systematic review of the efficacy of different management strategies. *Canadian Journal of Psychiatry*. 1999;44(10):1007-1016.
24. American Academy of Pediatrics, Subcommittee on Attention-Deficit/Hyperactivity Disorder, Committee on Quality Improvement. Clinical Practice Guideline: Treatment of the School-Aged Child With Attention-Deficit/Hyperactivity Disorder. *Pediatrics*. 2001;108(4):1033-1044.
25. Barrickman LL, Perry PJ, Allen AJ, et al. Bupropion versus methylphenidate in the treatment of attention-deficit hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1995;34(5):649-657.
26. Bergman A, Winters L, Cornblatt B. Methylphenidate: Effects on sustained attention. *Greenhill, Laurence L (Ed); Osman, Betty B (Ed) (1991) Ritalin: Theory and patient management (pp 223-231) 338pp*; 1991.
27. Borcharding BG, Keysor CS, Rapoport JL, Elia J, Amass J. Motor/vocal tics and compulsive behaviors on stimulant drugs: is there a common vulnerability? *Psychiatry Research*. 1990;33(1):83-94.
28. Buitelaar JK, van der Gaag RJ, Swaab-Barneveld H, Kuiper M. Pindolol and methylphenidate in children with attention-deficit hyperactivity disorder. Clinical efficacy and side-effects. *Journal of Child Psychology & Psychiatry & Allied Disciplines*. 1996;37(5):587-595.
29. Bussing R, Zima BT, Mason D, Hou W, Garvan CW, Forness S. Use and persistence of pharmacotherapy for elementary school students with attention-deficit/hyperactivity disorder. *Journal of Child & Adolescent Psychopharmacology*. 2005;15(1):78-87.
30. Chronis AM, Pelham WE, Gnagy EM, Roberts JE, Aronoff HR. The impact of late-afternoon stimulant dosing for children with ADHD on parent and parent-child domains. *Journal of Clinical Child & Adolescent Psychology*. Mar 2003;32(1):118-126.
31. Connor DF, Barkley RA, Davis HT. A pilot study of methylphenidate, clonidine, or the combination in ADHD comorbid with aggressive oppositional defiant or conduct disorder. *Clinical Pediatrics*. 2000;39(1):15-25.
32. Cox DJ, Humphrey JW, Merkel RL, Penberthy JK, Kovatchev B. Controlled-release methylphenidate improves attention during on-road driving by adolescents with attention-deficit/hyperactivity disorder. *Journal of the American Board of Family Practice*. 2004;17(4):235-239.
33. Efron D, Jarman FC, Barker MJ. Child and parent perceptions of stimulant medication treatment in attention deficit hyperactivity disorder. *Journal of Paediatrics & Child Health*. 1998;34(3):288-292.
34. Elia J, Borcharding BG, Potter WZ, Mefford IN, Rapoport JL, Keysor CS. Stimulant drug treatment of hyperactivity: biochemical correlates. *Clinical Pharmacology & Therapeutics*. 1990;48(1):57-66.
35. Elia J, Welsh PA, Gullotta CS, Rapoport JL. Classroom academic performance: improvement with both methylphenidate and dextroamphetamine in ADHD boys. *Journal of Child Psychology & Psychiatry & Allied Disciplines*. 1993;34(5):785-804.
36. Faraone SV, Short EJ, Biederman J, Findling RL, Roe C, Manos MJ. Efficacy of Adderall and methylphenidate in attention deficit hyperactivity disorder: a drug-placebo and drug-drug response curve analysis of a naturalistic study. *International Journal of Neuropsychopharmacology*. 2002;5(2):121-129.
37. Huestis RD, Arnold LE, Smeltzer DJ. Caffeine versus methylphenidate and d-amphetamine in minimal brain dysfunction: a double-blind comparison. *American Journal of Psychiatry*. 1975;132(8):868-870.

38. Lage M, Hwang P. Effect of methylphenidate formulation for attention deficit hyperactivity disorder on patterns and outcomes of treatment. *Journal of Child & Adolescent Psychopharmacology*. December 2004 2004;14:575-581.
39. Lopez F, Silva R, Pestreich L, Muniz R. Comparative efficacy of two once daily methylphenidate formulations (Ritalin LA and Concerta) and placebo in children with attention deficit hyperactivity disorder across the school day. *Paediatric Drugs*. 2003;5(8):545-555.
40. Manos MJ, Short EJ, Findling RL. Differential effectiveness of methylphenidate and Adderall in school-age youths with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1999;38(7):813-819.
41. Marcus SC, Wan GJ, Kemner JE, Olfson M. Continuity of Methylphenidate Treatment for Attention-Deficit/Hyperactivity Disorder. *Arch Pediatr Adolesc Med*. June 1, 2005 2005;159(6):572-578.
42. MTA Cooperative Group. National Institute of Mental Health Multimodal Treatment Study of ADHD Follow-up: 24-Month Outcomes of Treatment Strategies for Attention-Deficit/Hyperactivity Disorder. *Pediatrics*. April 1, 2004 2004;113(4):754-761.
43. Pelham WE, Aronoff HR, Midlam JK, et al. A comparison of ritalin and adderall: efficacy and time-course in children with attention-deficit/hyperactivity disorder. *Pediatrics*. 1999b;103(4):e43.
44. Schmidt ME, Kruesi MJ, Elia J, et al. Effect of dextroamphetamine and methylphenidate on calcium and magnesium concentration in hyperactive boys. *Psychiatry Research*. 1994;54(2):199-210.
45. Sharp WS, Walter JM, Marsh WL, Ritchie GF, Hamburger SD, Castellanos FX. ADHD in girls: clinical comparability of a research sample. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1999;38(1):40-47.
46. Simpson RL, Reece CA, Kauffman R, Jones F. Stimulant medications and the classroom attention-to-task and deviant social behaviors of twelve hyperactive males. *Learning Disability Quarterly*. 1980;3(1):19-27.
47. The Tourette's Syndrome Study Group. Treatment of ADHD in children with tics: a randomized controlled trial. [comment]. *Neurology*. 2002;58(4):527-536.
48. van der Meere J, Gunning B, Stemerink N. The effect of methylphenidate and clonidine on response inhibition and state regulation in children with ADHD. *Journal of Child Psychology & Psychiatry & Allied Disciplines*. 1999;40(2):291-298.
49. Schleifer M, Weiss G, Cohen N, Elman M, Cvejic H, Kruger E. Hyperactivity in preschoolers and the effect of methylphenidate. *American Journal of Orthopsychiatry*. 1975;45(1):38-50.
50. Barkley RA. The effects of methylphenidate on the interactions of preschool ADHD children with their mothers. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1988;27(3):336-341.
51. Musten LM, Firestone P, Pisterman S, Bennett S, Mercer J. Effects of methylphenidate on preschool children with ADHD: cognitive and behavioral functions. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1997;36(10):1407-1415.
52. Firestone P, Musten LM, Pisterman S, Mercer J, Bennett S. Short-term side effects of stimulant medication are increased in preschool children with attention-deficit/hyperactivity disorder: a double-blind placebo-controlled study. *Journal of Child & Adolescent Psychopharmacology*. 1998;8(1):13-25.
53. Conners CK. Controlled trial of methylphenidate in preschool children with minimal brain dysfunction. *Int J Mental Health*. 1975;4:61-75.
54. Chacko A, Pelham WE, Gnagy EM, et al. Stimulant medication effects in a summer treatment program among young children with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2005;44(3):249-257.

55. *Table 4: Annual Estimates of the Population by Race Alone and Hispanic or Latino Origin for the United States and States*: Population Division, U.S. Census Bureau; July 1, 2004 (SC-EST2004-04).
56. American Academy of Pediatrics. Committee on Quality Improvement and Subcommittee on Attention-Deficit/Hyperactivity Disorder Clinical Practice Guideline: Diagnosis and Evaluation of the Child With Attention-Deficit/Hyperactivity Disorder. *Pediatrics*. May 2000(105):1158-1170.
57. Fitzpatrick PA, Klorman R, Brumaghim JT, Borgstedt AD. Effects of sustained-release and standard preparations of methylphenidate on attention deficit disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1992;31(2):226-234.
58. Pelham WE, Jr., Sturges J, Hoza J, et al. Sustained release and standard methylphenidate effects on cognitive and social behavior in children with attention deficit disorder. *Pediatrics*. 1987;80(4):491-501.
59. Pelham WE, Gnagy EM, Burrows-Maclean L, et al. Once-a-day Concerta methylphenidate versus three-times-daily methylphenidate in laboratory and natural settings.[see comment]. *Pediatrics*. 2001;107(6).
60. Cox DJ, Merkel RL, Penberthy JK, Kovatchev B, Hankin CS. Impact of methylphenidate delivery profiles on driving performance of adolescents with attention-deficit/hyperactivity disorder: a pilot study. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2004;43(3):269-275.
61. Wolraich ML, Greenhill LL, Pelham W, et al. Randomized, controlled trial of OROS methylphenidate once a day in children with attention-deficit/hyperactivity disorder. *Pediatrics*. 2001;108(4):883-892.
62. Whitehouse D, Shah U, Palmer FB. Comparison of sustained-release and standard methylphenidate in the treatment of minimal brain dysfunction. *Journal of Clinical Psychiatry*. 1980;41(8):282-285.
63. Pelham WE, Jr., Greenslade KE, Vodde-Hamilton M, et al. Relative efficacy of long-acting stimulants on children with attention deficit-hyperactivity disorder: a comparison of standard methylphenidate, sustained-release methylphenidate, sustained-release dextroamphetamine, and pemoline. *Pediatrics*. 1990;86(2):226-237.
64. Dopfner M, Gerber WD, Banaschewski T, et al. Comparative efficacy of once-a-day extended-release methylphenidate, two-times-daily immediate-release methylphenidate, and placebo in a laboratory school setting. *European child & adolescent psychiatry*. 2004;13 Suppl 1:I93-101.
65. Anonymous. Sustained-release methylphenidate: new preparations. New pharmaceutical forms: a slight advantage for a small number of children. *Prescrire international*. 2004;13(74):203-206.
66. Lage M, Hwang P. Effect of methylphenidate formulation for attention deficit hyperactivity disorder on patterns and outcomes of treatment. *Journal of Child & Adolescent Psychopharmacology*. 2004;14(4):575-581.
67. Sonuga-Barke EJ, Swanson JM, Coghill D, DeCory HH, Hatch SJ. Efficacy of two once-daily methylphenidate formulations compared across dose levels at different times of the day: preliminary indications from a secondary analysis of the COMACS study data. *BMC psychiatry [electronic resource]*. 2004;4(1):28.
68. Swanson JM, Wigal SB, Wigal T, et al. A comparison of once-daily extended-release methylphenidate formulations in children with attention-deficit/hyperactivity disorder in the laboratory school (the Comacs Study). *Pediatrics*. 2004;113(3 Pt 1):e206-216.
69. Greenhill LL, Findling RL, Swanson JM, Group AS. A double-blind, placebo-controlled study of modified-release methylphenidate in children with attention-deficit/hyperactivity disorder. *Pediatrics*. 2002;109(3):e39.
70. Arnold LE, Christopher J, Huestis R, Smeltzer DJ. Methylphenidate vs dextroamphetamine vs caffeine in minimal brain dysfunction: controlled comparison by placebo washout design with Bayes' analysis. *Archives of General Psychiatry*. 1978;35(4):463-473.

71. Efron D, Jarman F, Barker M. Side effects of methylphenidate and dexamphetamine in children with attention deficit hyperactivity disorder: a double-blind, crossover trial. *Pediatrics*. 1997a;100(4):662-666.
72. Elia J, Borchering BG, Rapoport JL, Keysor CS. Methylphenidate and dextroamphetamine treatments of hyperactivity: are there true nonresponders? *Psychiatry Research*. 1991;36(2):141-155.
73. Kauffman RE, Smith-Wright D, Reese CA, Simpson R, Jones F. Medication compliance in hyperactive children. *Pediatric Pharmacology*. 1981;1(3):231-237.
74. Gross MD. A comparison of dextro-amphetamine and racemic-amphetamine in the treatment of the hyperkinetic syndrome or minimal brain dysfunction. *Diseases of the Nervous System*. 1976;37(1):14-16.
75. Castellanos FX, Giedd JN, Elia J, et al. Controlled stimulant treatment of ADHD and comorbid Tourette's syndrome: effects of stimulant and dose. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1997;36(5):589-596.
76. Charles L, Schain R. A Four-Year Follow-Up Study of the Effects of Methylphenidate on the Behavior and Academic Achievement of Hyperactive Children. *Journal of Abnormal Child Psychology*. 1981;9(4):495-505.
77. Conrad WG, Dworkin ES, Shai A, Tobiessen JE. Effects of amphetamine therapy and prescriptive tutoring on the behavior and achievement of lower class hyperactive children. *Journal of Learning Disabilities*. 1971;4(9):45-53.
78. Ialongo NS, Horn WF, Pascoe JM, et al. The effects of a multimodal intervention with attention-deficit hyperactivity disorder children: a 9-month follow-up. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1993;32(1):182-189.
79. Kupietz SS, Winsberg BG, Richardson E, Maitinsky S, et al. Effects of methylphenidate dosage in hyperactive reading-disabled children: I. Behavior and cognitive performance effects. *Journal of the American Academy of Child & Adolescent Psychiatry*. Jan 1988;27(1):70-77.
80. Jensen PS, Arnold LE, Richters JE, et al. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. *Archives of General Psychiatry*. 1999;56(12):1073-1086.
81. Firestone P, Crowe D, Goodman JT, McGrath P. Vicissitudes of follow-up studies: differential effects of parent training and stimulant medication with hyperactives. *American Journal of Orthopsychiatry*. 1986;56(2):184-194.
82. Brown RT, Borden KA, Clingerman SR. Pharmacotherapy in ADD adolescents with special attention to multimodality treatments. *Psychopharmacology Bulletin*. 1985;21(2):192-211.
83. Brown RT, Borden KA, Wynne ME, Schleser R, Clingerman SR. Methylphenidate and cognitive therapy with ADD children: a methodological reconsideration. *Journal of Abnormal Child Psychology*. 1986;14(4):481-497.
84. Arnold LE, Lindsay RL, Conners CK, et al. A double-blind, placebo-controlled withdrawal trial of dexamethylphenidate hydrochloride in children with attention deficit hyperactivity disorder. *Journal of Child and Adolescent Psychopharmacology*. 2004;14(4):542-554.
85. Sleator EK, Von Neumann A, Sprague RL. Hyperactive children. A continuous long-term placebo-controlled follow-up. *JAMA*. 1974;229(3):316-317.
86. Zeiner P. Do the beneficial effects of extended methylphenidate treatment in boys with attention-deficit hyperactivity disorder dissipate rapidly during placebo treatment? *Nordic Journal of Psychiatry*. 1999;53(1):55-60.
87. Pelham WE, Gnagy EM, Chronis AM, et al. A comparison of morning-only and morning/late afternoon Adderall to morning-only, twice-daily, and three times-daily methylphenidate in children with attention-deficit/hyperactivity disorder. *Pediatrics*. 1999a;104(6):1300-1311.
88. Pliszka SR, Browne RG, Olvera RL, Wynne SK. A double-blind, placebo-controlled study of Adderall and methylphenidate in the treatment of attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2000;39(5):619-626.

89. Barkley RA, Connor DF, Kwasnik D. Challenges to determining adolescent medication response in an outpatient clinical setting: Comparing Adderall and methylphenidate for ADHD. *Journal of Attention Disorders*. Aug 2000;4(2):102-113.
90. James RS, Sharp WS, Bastain TM, et al. Double-blind, placebo-controlled study of single-dose amphetamine formulations in ADHD. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2001;40(11):1268-1276.
91. Wigal S, Swanson JM, Feifel D, et al. A double-blind, placebo-controlled trial of dextmethylphenidate hydrochloride and d,l-threo-methylphenidate hydrochloride in children with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2004;43(11):1406-1414.
92. Rugino TA, Samscock TC. Modafinil in children with attention-deficit hyperactivity disorder. *Pediatric Neurology*. 2003;29(2):136-142.
93. Kratochvil CJ, Heiligenstein JH, Dittmann R, et al. Atomoxetine and methylphenidate treatment in children with ADHD: a prospective, randomized, open-label trial. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2002;41(7):776-784.
94. Spencer T, Heiligenstein JH, Biederman J, et al. Results from 2 proof-of-concept, placebo-controlled studies of atomoxetine in children with attention-deficit/hyperactivity disorder. *Journal of Clinical Psychiatry*. 2002;63(12):1140-1147.
95. Kemner J, Starr H, Ciccone P, Hooper Wood C, Crockett S. Outcomes of OROS methylphenidate compared with atomoxetine in children with ADHD: a multi-center, randomized, prospective study. *Advances in Therapy*. 2005;22(5):498-451.
96. Wigal SB, McGough JJ, McCracken JT, et al. A laboratory school comparison of mixed amphetamine salts extended release (Adderall XR) and atomoxetine (Strattera) in school-aged children with attention deficit/hyperactivity disorder. *Journal of Attention Disorders*. 2005;9(1):275-289.
97. Michelson D, Faries D, Wernicke J, et al. Atomoxetine in the treatment of children and adolescents with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled, dose-response study. *Pediatrics*. 2001;108(5):e83.
98. Michelson D, Allen AJ, Busner J, et al. Once-daily atomoxetine treatment for children and adolescents with attention deficit hyperactivity disorder: a randomized, placebo-controlled study. *American Journal of Psychiatry*. 2002;159(11):1896-1901.
99. Kelsey DK, Sumner CR, Casat CD, et al. Once-daily atomoxetine treatment for children with attention-deficit/hyperactivity disorder, including an assessment of evening and morning behavior: a double-blind, placebo-controlled trial. *Pediatrics*. 2004;114(1).
100. Michelson D, Buitelaar JK, Danckaerts M, et al. Relapse prevention in pediatric patients with ADHD treated with atomoxetine: a randomized, double-blind, placebo-controlled study. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2004;43(7):896-904.
101. Kaplan S, Heiligenstein J, West S, et al. Efficacy and safety of atomoxetine in childhood attention-deficit/hyperactivity disorder with comorbid oppositional defiant disorder. *Journal of attention disorders*. 2004;8(2):45-52.
102. Weiss M, Tannock R, Kratochvil C, et al. A randomized, placebo-controlled study of once-daily atomoxetine in the school setting in children with ADHD. *Journal of the American Academy of Child & Adolescent Psychiatry*. Jul 2005;44(7):647-655.
103. Brown RT, Sexson SB. A controlled trial of methylphenidate in black adolescents. Attentional, behavioral, and physiological effects. *Clinical Pediatrics*. 1988;27(2):74-81.
104. Pelham WE, Vodde-Hamilton M, Murphy DA, Greenstein J, Vallano G. The effects of methylphenidate on ADHD adolescents in recreational, peer group, and classroom settings. *Journal of Clinical Child Psychology*. 1991;20(3):293-300.
105. Varley CK. Effects of methylphenidate in adolescents with attention deficit disorder. *Journal of the American Academy of Child Psychiatry*. 1983;22(4):351-354.

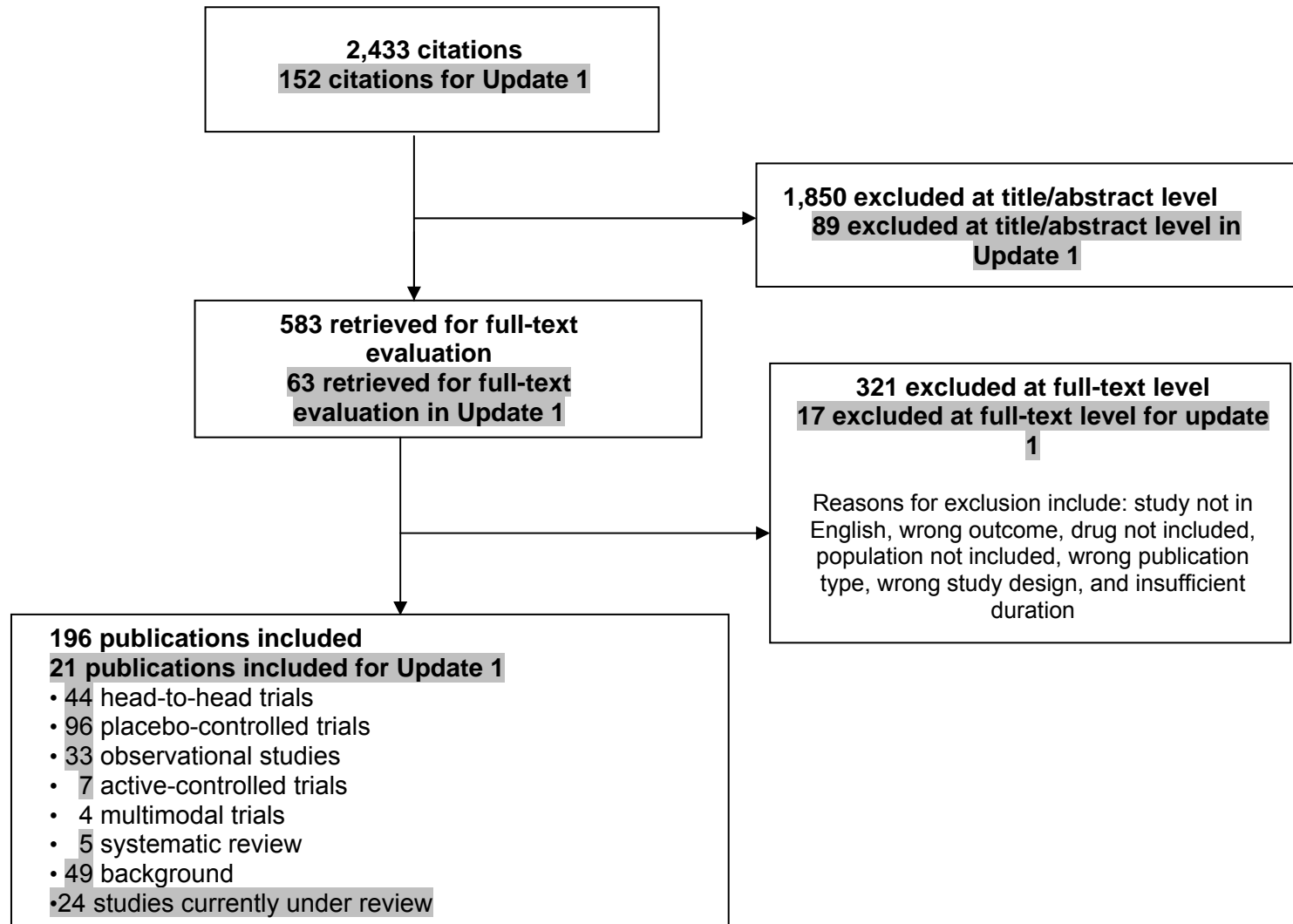
106. Klorman R, Coons HW, Borgstedt AD. Effects of methylphenidate on adolescents with a childhood history of attention deficit disorder: I. Clinical findings. *Journal of the American Academy of Child & Adolescent Psychiatry*. May 1987;26(3):363-367.
107. Coons HW, Klorman R, Borgstedt AD. Effects of methylphenidate on adolescents with a childhood history of attention deficit disorder: II. Information processing. *Journal of the American Academy of Child & Adolescent Psychiatry*. May 1987;26(3):368-374.
108. Smith BH, Pelham WE, Evans S, et al. Dosage effects of methylphenidate on the social behavior of adolescents diagnosed with attention-deficit hyperactivity disorder. *Experimental & Clinical Psychopharmacology*. 1998;6(2):187-204.
109. Klorman R, Brumaghim JT, Fitzpatrick PA, Borgstedt AD. Clinical effects of a controlled trial of methylphenidate on adolescents with attention deficit disorder [comment]. *Journal of the American Academy of Child & Adolescent Psychiatry*. Sep 1990;29(5):702-709.
110. Klorman R, Brumaghim JT, Fitzpatrick PA, Borgstedt AD. Methylphenidate speeds evaluation processes of attention deficit disorder adolescents during a continuous performance test. *Journal of Abnormal Child Psychology*. 1991;19(3):263-283.
111. Klorman R, Brumaghim JT, Fitzpatrick PA, Borgstedt AD. Methylphenidate reduces abnormalities of stimulus classification in adolescents with attention deficit disorder. *Journal of Abnormal Psychology*. 1992;101(1):130-138.
112. Ahmann PA, Waltonen SJ, Olson KA, Theye FW, Van Erem AJ, LaPlant RJ. Placebo-controlled evaluation of Ritalin side effects. *Pediatrics*. 1993;91(6):1101-1106.
113. Evans SW, Pelham WE, Smith BH, et al. Dose-response effects of methylphenidate on ecologically valid measures of academic performance and classroom behavior in adolescents with ADHD. *Experimental & Clinical Psychopharmacology*. 2001;9(2):163-175.
114. Potter AS, Newhouse PA. Effects of acute nicotine administration on behavioral inhibition in adolescents with attention-deficit/hyperactivity disorder. *Psychopharmacology*. 2004;176(2):182-194.
115. Lerer RJ, Lerer MP. Response of adolescents with minimal brain dysfunction to methylphenidate. *Journal of Learning Disabilities*. 1977;10(4):35-40.
116. Paternite CE, Loney J, Salisbury H, Whaley MA. Childhood inattention-overactivity, aggression, and stimulant medication history as predictors of young adult outcomes. *Journal of Child & Adolescent Psychopharmacology*. 1999;9(3):169-184.
117. Matochik JA, Liebenauer LL, King AC, Szymanski HV, Cohen RM, Zametkin AJ. Cerebral Glucose Metabolism in Adults With Attention Deficit Hyperactivity Disorder After Chronic Stimulant Treatment. *American Journal of Psychiatry*. 1994;151(5):658-664.
118. Mattes JA, Boswell L, Oliver H. Methylphenidate effects on symptoms of attention deficit disorder in adults. *Archives of General Psychiatry*. 1984;41(11):1059-1063.
119. Spencer T, Wilens T, Biederman J, Faraone SV, Ablon JS, Lapey K. A double-blind, crossover comparison of methylphenidate and placebo in adults with childhood-onset attention-deficit hyperactivity disorder. *Archives of General Psychiatry*. 1995;52(6):434-443.
120. Wender PH, Reimherr FW, Wood D, Ward M. A controlled study of methylphenidate in the treatment of attention deficit disorder, residual type, in adults. *American Journal of Psychiatry*. 1985;142(5):547-552.
121. Wender PH, Reimherr FW, Wood DR. Attention deficit disorder ('minimal brain dysfunction') in adults. A replication study of diagnosis and drug treatment. *Archives of General Psychiatry*. 1981;38(4):449-456.
122. Taylor FB, Russo J. Efficacy of modafinil compared to dextroamphetamine for the treatment of attention deficit hyperactivity disorder in adults. *Journal of Child & Adolescent Psychopharmacology*. 2000;10(4):311-320.
123. Taylor FB, Russo J. Comparing guanfacine and dextroamphetamine for the treatment of adult attention-deficit/hyperactivity disorder. *Journal of Clinical Psychopharmacology*. 2001;21(2):223-228.

124. Paterson R, Douglas C, Hallmayer J, Hagan M, Krupenia Z. A randomised, double-blind, placebo-controlled trial of dexamphetamine in adults with attention deficit hyperactivity disorder.[comment]. *Australian & New Zealand Journal of Psychiatry*. 1999;33(4):494-502.
125. Kuperman S, Perry PJ, Gaffney GR, et al. Bupropion SR vs. methylphenidate vs. placebo for attention deficit hyperactivity disorder in adults. *Annals of Clinical Psychiatry*. 2001;13(3):129-134.
126. Wood DR, Reimherr FW, Wender PH, Johnson GE. Diagnosis and treatment of minimal brain dysfunction in adults: a preliminary report. *Archives of General Psychiatry*. 1976;33(12):1453-1460.
127. Tenenbaum S, Paull JC, Sparrow EP, Dodd DK, Green L. An experimental comparison of Pycnogenol and methylphenidate in adults with Attention-Deficit/Hyperactivity Disorder (ADHD). *Journal of Attention Disorders*. 2002;6(2):49-60.
128. Schubiner H, Saules KK, Arfken CL, et al. Double-blind placebo-controlled trial of methylphenidate in the treatment of adult ADHD patients with comorbid cocaine dependence. *Experimental & Clinical Psychopharmacology*. 2002;10(3):286-294.
129. Levin ED, Conners CK, Silva D, Canu W, March J. Effects of chronic nicotine and methylphenidate in adults with attention deficit/hyperactivity disorder. *Experimental & Clinical Psychopharmacology*. 2001;9(1):83-90.
130. Kinsbourne M, De Quiros GB, Rufo DT. Adult ADHD: Controlled medication assessment. *Annals of the New York Academy of Sciences*. 2001;931:287-296.
131. Gualtieri CT. Attention Deficit Disorder in Adults. *Clinical Neuropharmacology*. 1985;8(4):343-356.
132. Cox DJ, Merkel RL, Kovatchev B, Seward R. Effect of stimulant medication on driving performance of young adults with attention-deficit hyperactivity disorder: a preliminary double-blind placebo controlled trial.[comment]. *Journal of Nervous & Mental Disease*. 2000;188(4):230-234.
133. Bouffard R, Hechtman L, Minde K, Iaboni-Kassab F. The efficacy of 2 different dosages of methylphenidate in treating adults with attention-deficit hyperactivity disorder. *Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie*. 2003;48(8):546-554.
134. Spencer T, Biederman J, Wilens T, et al. A large, double-blind, randomized clinical trial of methylphenidate in the treatment of adults with attention-deficit/hyperactivity disorder. *Biological Psychiatry*. 2005;57(5):456-463.
135. Spencer T, Biederman J, Wilens T, et al. Efficacy of a mixed amphetamine salts compound in adults with attention-deficit/hyperactivity disorder.[comment]. *Archives of General Psychiatry*. 2001;58(8):775-782.
136. Spencer T, Biederman J, Wilens T, et al. Effectiveness and tolerability of tomoxetine in adults with attention deficit hyperactivity disorder. *American Journal of Psychiatry*. 1998;155(5):693-695.
137. Michelson D, Adler L, Spencer T, et al. Atomoxetine in adults with ADHD: two randomized, placebo-controlled studies. *Biological Psychiatry*. 2003;53(2):112-120.
138. Turner DC, Clark L, Dowson J, Robbins TW, Sahakian BJ. Modafinil improves cognition and response inhibition in adult attention-deficit/hyperactivity disorder. *Biological Psychiatry*. 2004;55(10):1031-1040.
139. Wernicke JF, Adler L, Spencer T, et al. Changes in Symptoms and Adverse Events after Discontinuation of Atomoxetine in Children and Adults with Attention Deficit/Hyperactivity Disorder: A Prospective, Placebo-Controlled Assessment. *Journal of Clinical Psychopharmacology*. 2004;24(1):30-35.
140. Barkley RA, Murphy KR, O'Connell T, Connor DF. Effects of two doses of methylphenidate on simulator driving performance in adults with attention deficit hyperactivity disorder. *Journal of safety research*. 2005;36(2):121-131.

141. Boonstra AM, Kooij JJ, Oosterlaan J, Sergeant JA, Buitelaar JK. Does methylphenidate improve inhibition and other cognitive abilities in adults with childhood-onset ADHD? *Journal of clinical and experimental neuropsychology : official journal of the International Neuropsychological Society*. 2005;27(3):278-298.
142. Kooij JJ, Burger H, Boonstra AM, Van der Linden PD, Kalma LE, Buitelaar JK. Efficacy and safety of methylphenidate in 45 adults with attention-deficit/hyperactivity disorder. A randomized placebo-controlled double-blind cross-over trial. *Psychological medicine*. 2004;34(6):973-982.
143. Turner DC, Blackwell AD, Dowson JH, McLean A, Sahakian BJ. Neurocognitive effects of methylphenidate in adult attention-deficit/hyperactivity disorder. *Psychopharmacology*. Mar 2005;178(2-3):286-295.
144. Weiss G, Kruger E, Danielson U, Elman M. Effect of long-term treatment of hyperactive children with methylphenidate. *Canadian Medical Association Journal*. 1975;112(2):159-165.
145. Hechtman L, Weiss G, Perlman T. Young adult outcome of hyperactive children who received long-term stimulant treatment. *Journal of the American Academy of Child Psychiatry*. 1984;23(3):261-269.
146. Klein RG, Landa B, Mattes JA, Klein DF. Methylphenidate and growth in hyperactive children. A controlled withdrawal study. *Archives of General Psychiatry*. 1988;45(12):1127-1130.
147. Brown RT, Sexson SB. Effects of methylphenidate on cardiovascular responses in attention deficit hyperactivity disorder adolescents. *Journal of Adolescent Health Care*. 1989;10(3):179-183.
148. Spencer TJ, Newcorn JH, Kratochvil CJ, Ruff D, Michelson D, Biederman J. Effects of Atomoxetine on Growth After 2-Year Treatment Among Pediatric Patients With Attention-Deficit/Hyperactivity Disorder. *Pediatrics*. 2005;116(1):e74-80.
149. Brehaut JC, Miller A, Raina P, McGrail KM. Childhood behavior disorders and injuries among children and youth: a population-based study. *Pediatrics*. 2003;111(2):262-269.
150. Gadow KD, Sverd J, Sprafkin J, Nolan EE, Grossman S. Long-term methylphenidate therapy in children with comorbid attention-deficit hyperactivity disorder and chronic multiple tic disorder.[comment]. *Archives of General Psychiatry*. 1999;56(4):330-336.
151. Quinn PO, Rapoport JL. One-year follow-up of hyperactive boys treated with imipramine or methylphenidate. *American Journal of Psychiatry*. 1975;132(3):241-245.
152. Mattes JA, Gittelman R. Growth of hyperactive children on maintenance regimen of methylphenidate. *Archives of General Psychiatry*. 1983;40(3):317-321.
153. Wernicke JF, Faries D, Girod D, et al. Cardiovascular effects of atomoxetine in children, adolescents, and adults. *Drug Safety*. 2003;26(10):729-740.
154. Gross MD. Growth of hyperkinetic children taking methylphenidate, dextroamphetamine, or imipramine/desipramine. *Pediatrics*. 1976;58:423-431.
155. Safer D, Allen R, Barr E. Depression of growth in hyperactive children on stimulant drugs. *New England Journal of Medicine*. 1972;287(5):217-220.
156. Satterfield JH. Growth of hyperactive children treated with methylphenidate. *Archives of General Psychiatry*. 1979;36:212-217.
157. McNutt BA, Ballard JE, Boileau RA. The effects of long-term stimulant medication on growth and body composition of hyperactive children. *Psychopharmacology Bulletin*. 1976;12(2):13-15.
158. Wilens T, Pelham W, Stein M, et al. ADHD Treatment With Once-Daily OROS Methylphenidate: Interim 12-Month Results From a Long-Term Open-Label Study. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2003;42(4):424-433.
159. Millichap JG. Growth of hyperactive children treated with methylphenidate: A possible growth stimulant effect. In: Millichap JG, ed. *Learning Disabilities and Related Disorders*. Chicago: Year Book Medical Publishers Inc.; 1977:151-154.
160. Horrigan JP, Barnhill LJ. Low-dose amphetamine salts and adult attention-deficit/hyperactivity disorder. *Journal of Clinical Psychiatry*. 2000;61(6):414-417.

161. Safer D, Allen R. Factors influencing the suppressant effects of two stimulant drugs on the growth of hyperactive children. *Pediatrics*. 1973;51(4):660-667.
162. Zeiner. Body Growth and Cardiovascular Function after Extended Treatment (1.75 Years) with Methylphenidate in Boys with Attention-Deficit Hyperactivity Disorder. *Journal of Child and Adolescent Psychopharmacology*. 1995;5(2):129-138.
163. Safer DJ, Allen RP, Barr E. Growth rebound after termination of stimulant drugs. *Journal of Pediatrics*. 1975;86(1):113-116.
164. Kratochvil CJ, Bohac D, Harrington M, Baker N, May D, Burke WJ. An open-label trial of tomoxetine in pediatric attention deficit hyperactivity disorder. *Journal of Child & Adolescent Psychopharmacology*. 2001;11(2):167-170.
165. Rapport MD, Moffitt C. Attention deficit/hyperactivity disorder and methylphenidate. A review of height/weight, cardiovascular, and somatic complaint side effects. *Clin Psychol Rev*. 2002;22:1107-1131.
166. McGough JJ, Biederman J, Wigal SB, et al. Long-term tolerability and effectiveness of once-daily mixed amphetamine salts (Adderall XR) in children with ADHD. *Journal of the American Academy of Child & Adolescent Psychiatry*. Jun 2005;44(6):530-538.
167. Law SF, Schachar RJ. Do typical clinical doses of methylphenidate cause tics in children treated for attention-deficit hyperactivity disorder? *Journal of the American Academy of Child & Adolescent Psychiatry*. 1999;38(8):944-951.
168. Barkley RA, Fischer M, Smallish L, Fletcher K. Does the treatment of attention-deficit/hyperactivity disorder with stimulants contribute to drug use/abuse? A 13-year prospective study.[see comment]. *Pediatrics*. 2003;111(1):97-109.
169. Blouin AGA, Bornstein RA, Trites RL. Teenage Alcohol use among hyperactive children: a five year follow-up study. *Journal of Pediatric Psychology*. 1978;3(4):188-194.
170. Musser CJ, Ahmann PA, Theye FW, Mundt P, Broste SK, Mueller-Rizner N. Stimulant use and the potential for abuse in Wisconsin as reported by school administrators and longitudinally followed children. *Journal of Developmental & Behavioral Pediatrics*. 1998;19(3):187-192.
171. Bangs ME, Tauscher-Wisniewski S, Polzer J, et al. Meta-analysis of Suicide-related Events in Atomoxetine-treated patients. Paper presented at: FDA Pediatric Advisory Committee Meeting (March 22, 2006), 2005.
172. El-Zein RA, Abdel-Rahman SZ, Hay MJ, et al. Cytogenetic effects in children treated with methylphenidate. *Cancer Lett*. Dec 18 2005;230(2):284-291.
173. Starr HL, Kemner J. Multicenter, randomized, open-label study of OROS methylphenidate versus atomoxetine: treatment outcomes in African-American children with ADHD. *Journal of the National Medical Association*. 2005;97(10 Suppl):11S-16S.
174. Barkley RA. Hyperactive girls and boys: stimulant drug effects on mother-child interactions. *Journal of Child Psychology & Psychiatry & Allied Disciplines*. 1989;30(3):379-390.
175. Pelham WE, Jr., Walker JL, Sturges J, Hoza J. Comparative effects of methylphenidate on ADD girls and ADD boys. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1989;28(5):773-776.
176. Biederman J, Heiligenstein JH, Faries DE, et al. Efficacy of atomoxetine versus placebo in school-age girls with attention-deficit/hyperactivity disorder. *Pediatrics*. 2002;110(6):e75.
177. Sverd J, Gadow KD, Nolan EE, Sprafkin J, Ezor SN. Methylphenidate in hyperactive boys with comorbid tic disorder: I. Clinic evaluations. Chase, Thomas N (Ed); Friedhoff, Arnold J (Ed); et al (1992) *Tourette syndrome: Genetics, neurobiology, and treatment Advances in neurology*, Vol 58 (pp 271-281) xix, 377pp; 1992.
178. Gadow KD, Nolan E, Sprafkin J, Sverd J. School observations of children with attention-deficit hyperactivity disorder and comorbid tic disorder: effects of methylphenidate treatment. *Journal of Developmental & Behavioral Pediatrics*. 1995;16(3):167-176.

179. Handen BL, Breau AM, Gosling A, Ploof DL, Feldman H. Efficacy of methylphenidate among mentally retarded children with attention deficit hyperactivity disorder.[comment]. *Pediatrics*. 1990;86(6):922-930.
180. Handen BL, Feldman H, Gosling A, Breau AM, McAuliffe S. Adverse side effects of methylphenidate among mentally retarded children with ADHD. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1991;30(2):241-245.
181. Handen BL, Breau AM, Janosky J, McAuliffe S, Feldman H, Gosling A. Effects and noneffects of methylphenidate in children with mental retardation and ADHD. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1992;31(3):455-461.
182. Handen BL, McAuliffe S, Janosky J, Feldman H, et al. Methylphenidate in children with mental retardation and ADHD: Effects on independent play and academic functioning. *Journal of Developmental & Physical Disabilities*. Jun 1995;7(2):91-103.
183. Handen BL, McAuliffe S, Caro-Martinez L. Stimulant medication effects on learning in children with mental retardation and ADHD. *Journal of Developmental & Physical Disabilities*. Dec 1996;8(4):335-346.
184. Handen BL, Feldman HM, Lurier A, Murray PJ. Efficacy of methylphenidate among preschool children with developmental disabilities and ADHD. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1999;38(7):805-812.
185. Pearson DA, Santos CW, Roache JD, et al. Treatment effects of methylphenidate on behavioral adjustment in children with mental retardation and ADHD. *Journal of the American Academy of Child & Adolescent Psychiatry*. Feb 2003;42(2):209-216.
186. Agarwal V, Sitholey P, Kumar S, Prasad M. Double-blind, placebo-controlled trial of clonidine in hyperactive children with mental retardation. *Mental Retardation*. 2001;39(4):259-267.
187. Gross-Tsur V, Shalev RS, Badihi N, Manor O. Efficacy of Methylphenidate in Patients With Cerebral Palsy and Attention-Deficit Hyperactivity Disorder (ADHD). *Journal of Child Neurology*. Dec 2002;17(12):863-866.
188. Scheffer RE, Kowatch RA, Carmody T, Rush AJ. Randomized, placebo-controlled trial of mixed amphetamine salts for symptoms of comorbid ADHD in pediatric bipolar disorder after mood stabilization with divalproex sodium. *The American journal of psychiatry*. 2005;162(1):58-64.

Figure 1. Pharmacologic Treatments in ADHD: Drug Class Review Flow Diagram

Appendix A. Scales Used to Assess Efficacy and Adverse Events

The following narrative briefly describes the most commonly used assessment scales and summarizes methods of scoring and validation.

ADHD Behavior Checklist/ADHD Rating Scale evaluates inattentive and hyperactive-impulsive symptoms is based on DSM criteria for diagnosing ADHD. DSM-III uses a 14-item checklist while DSM-IV updated it to an 18-item checklist with two nine-item subscales. Items are rated for severity from zero to three according to how often the symptoms are present (0=never/rarely, 1=sometimes, 2=often, and 3=very often). The maximum scores are 42 points and 54 points for DSM-III and DSM-IV respectively. The test-retest reliability was demonstrated. The intraclass correlation coefficient was .90s ($p < 0.001$). The content validity and construct validity were proved as well. The checklist has established validity, reliability, and age-matched cut-off values (Achenbach & Edelbrock, 1983; DuPaul, 1998).

Barkley's Attention Deficit Hyperactivity Disorder Checklist and Scale is a self-report rating system that measures the occurrence of symptoms. The range of the scale is 0=never or rarely, 1=sometimes, 2=often, and 3=very often. The checklist is used a measurement to define symptoms of the disorder. No reliability or validity information available (Barkley & Murphy, 1998).

Barratt Impulsiveness Scale (BIS-10) is a 34-item scale that covers three types of impulsiveness: motor, cognitive, and non-planning. It consists of a four-point scale ranging ("rarely/never", "occasionally", "often", and "almost always/always"). These three factors are considered reliable under a study with an alpha coefficient range from 0.89 to 0.92. No validity information available (Barratt, 1985).

Brown ADD scale is a 40-item self report scale for assessing the executive function aspects associated with ADHD. The scale has been proved with good internal consistency and good test-retest reliability. The total score ranges from 0 to 120: patients with score >55 = highly probable ADHD; score 40-54 = 'probable' ADHD; score <40 = 'possible' ADHD (Brown, 1996).

Child Behavior Checklist (CBCL) originally had three axes, the parent report form, teacher report form, and self-report form for children over 11 years of age (Achenbach & Edelbrock, 1981). But it had been added to have two more axes, which are cognitive assessment and physical assessment from observations and interviews. It was demonstrated to have highly reliability and validity through various studies (Achenbach, 1999).

Children's Global Assessment Scale (CGAS) is an adaptation of the Global Assessment Scale (GAS). This scale is designed to measure the lowest level of functioning during a specific time period for children aged 4 to 16. Children are rated on a scale of 1 (needs constant supervision) to 100 (superior functioning) with anchor points in between. Scores above 70 indicate normal function. The CGAS has demonstrated discriminate validity ($P = .001$) in detecting the level of impairment between inpatients and outpatients. The CGAS has also demonstrated concurrent validity with the Conners ten-item Abbreviated Parent Checklist; the correlation was -0.25 ($P > .05$, $df=17$) when used in outpatients (Shaffer et al., 1983).

Children's Psychiatric Rating Scale (CPRS) is a comprehensive, 63-item scale that aims to assess a broad spectrum of psychopathology for children up to age 15. Therefore, items on the CPRS will have varying degrees of relevance when used in a specific diagnostic group. Each item is rated from one (not present) to seven (extremely severe). But unfortunately, we can't find any information about the reliability and validity of the scale (Fish 1985)

Continuous Performance Test (CPT) is a monitoring task in which subjects are given a series of visual or auditory stimuli and are asked to press a button when certain, infrequent target stimuli appear. There is no standardized version. There is usually a "low-level" version and a more sophisticated version where the stimulus may or may not be a target depending on what precedes it in the series. (Conners, Erhardt, & Sparrow, 1999; Epstein, Conners, Sitarenios, & Erhardt, 1998; Halperin, Greenblatt, Sharma, & Schwartz, 1991; Nuechterlein, 1983; Rosvold, Mirsky, Sarason, Bransome Jr, & Beck, 1956)

Clinical Global Impression Scale (CGI) is used in both children and adults and consists of three global scales for rating mental illness. The first two items (severity of illness and global improvement) are rated on a seven-point scale (1 = very much improved, 7 = very much worse). The third item (efficacy index) uses a matrix to rate the effectiveness of therapy in relation to adverse reactions (Guy, 1976).

Conners' Abbreviated Questionnaires (ASQ-P) is an abbreviated version of the CPRS. It contains 10 items only, and is known as the Hyperactivity Index. The intercorrelation of ASQ-P and CPRS-R was high as .87 in the hyperactive factor that demonstrated the ASQ-T's ability to identify children's hyperactive behaviors (Goyette, Conners, & Ulrich, 1978). Parents rate their child's symptoms from zero to three (0=not at all present, 1=just a little present, 2=pretty much present, 3=very much present), which yields a range of possible total scores between 0 and 30.

Conners' Abbreviated Questionnaires (ASQ-T) is an Abbreviated version of the CTRS. It contains 10 items only, and is known as the Hyperactivity Index. The intercorrelation of ASQ-T and CTRS-R was high from .79-.90 that demonstrated the ASQ-T's ability to identify children's problem behaviors (Goyette, Conners, & Ulrich, 1978)

Conners' Parent Rating Scale (CPRS) is a 93-item parent rating scale to evaluate children's psychiatric symptoms. It is the original version of the CPRS. Parents rate their child's symptoms from one to four (1=not at all present, 2=just a little present, 3=pretty much present, 4=very much present) (Conners, Erhardt, & Sparrow, 1999).

The 48-item Conners' Parent Rating Scale – Revised (CPRS-R) is a revised version of the 93-item Conners' Parent Rating Scale and includes norms down to age three. Parents rate their child's symptoms from zero to three (0=not at all present, 1=just a little present, 2=pretty much present, 3=very much present).(Goyette, Conners, & Ulrich, 1978)

Conners' Teacher Rating Scale (CTRS) is a 39-item teacher rating scale teachers to evaluate children's symptoms and behaviors before and after medication. The four-points scale (1-not at all, 2-just a little, 3-quite a bit, and 4-very much) was rated. Factor analysis was used to prove the stability of the scale. It is highly sensitive to drug effectiveness (Conners, Erhardt, & Sparrow, 1999). Teachers rate their child's symptoms from zero to three (0=not at all present, 1=just a little present, 2=pretty much present, 3=very much present), which yields a range of possible total scores between 0 and 30.

The 28-item Conners' Teacher Rating Scale – Revised (CTRS-R) is a revised version of the 48-item Conners' Teacher Rating Scale and includes norms down to age three. Teachers rate their child's symptoms from zero to three (0=not at all present, 1=just a little present, 2=pretty much present, 3=very much present). (Goyette, Conners, & Ulrich, 1978)

Copeland Symptom Checklist for Adult Attention Deficit Disorder, an 8-category, 63-item checklist with each item rated on a severity scale from 0 (symptoms not present) through 4 (very much present). It contains the information about cognitive, emotional and social symptoms. Its validity and reliability have been established, but we were unsuccessful in retrieving the original source, "Copeland Symptom Checklist for Adult Attention Deficit Disorders" (Copeland, 1989).

Global Assessment Scale (GAS) is a single rating scale for assessing the overall functioning of a patient. The scale values range from 1 to 100, with 1 being the hypothetical sickest person and 100 being the hypothetical healthiest person. There are ten equal intervals ranging from 1-10, 11-20, 21-30 and so on up until 91-100; if a patient falls in the upper two intervals, it is considered "positive mental health." A patient is rated based on observing his behavior during the preceding week and comparing it to the current time period, and adjustments are made to base on specific characteristics defined in each interval. The GAS is found to have good reliability based on five studies with an intraclass correlation coefficient range of 0.61 to 0.95 and an associated standard error of measurement range of 5.0 to 8.0 units. Strong concurrent validity was proved as well (Endicott, Spitzer, Fleiss, & Cohen, 1976).

"How I Feel" Questionnaire, a 28-item scale, is an adaptation of the van Kammen-Murphy Mood Scale, which has been proved to be sensitive to the effects of amphetamine. It uses 4-point scale: 0= "not at all"; 1="a little"; 2="some"; 3="a lot". No reliability or validity information is available (Rapoport et al., 1980).

Inattention/Overactivity With Aggression Conners' Teacher Rating Scale (IOWA CTRS) is revised from the 39-item Conners' Teacher scale. 10 items were devised to determine Inattention-Overactivity (IO) and aggression (A) behaviors. Teachers rate their child's symptoms from zero to three (0=not at all, 1=just a little, 2=pretty much, 3=very much). Coefficient alpha was tested as .89 for the IO scale and .86 for the A scale. They only tested the sensitivity and specificity scores of the IO scale, and the scores depend on the screen score being rated. Therefore, it recommended the use of an IO scale for at least 11 points for research purpose, and 7 points for clinical purpose (Loney & Milich, 1982). The differential validity of IO and A factors had been tested as well (Atkins, Pelham, & Licht, 1989).

Physician's Global Rating Scale is a seven-point rating of the overall functioning of a patient. The physician rates the patient improvement on a scale from -3 to +3. The number measures the change seen in the patient (-3=marked worsening, -2=moderate worsening, -1=slight worsening, 0=no change, +1=mild improvement, +2=moderate improvement, +3=marked improvement). No validity or reliability information is available (Wender, Reimherr, Wood, & Ward, 1985).

Physician's Target Symptom Scale is a four-point rating scale, ranging from 0 to 3 (0=not at all, 1=mild, 2=moderate, 3=marked). It measures specific symptoms of attention deficit disorder: conduct disorder (CD), disorganization, depression, temper, short attention span, and hyperactivity. No validity or reliability information is available (Wender, Reimherr, Wood, & Ward, 1985).

SCL-90 Rating Scale is a self-report clinical rating scale. It uses a 90-item checklist that covers nine symptom constructs, and three global indices of pathology. It consists of a five-point scale that measures the amount of distress a patient has felt to identify symptomatic behavior of psychiatric outpatients: 0=not at all, 1=a little bit, 2=moderately, 3=quite a bit, 4=extremely. There is evidence of strong convergent validity when compared to MMPI. No reliability information is available (Derogatis, Lipman, & Covi, 1973; Derogatis, Rickels, & Rock, 1976).

Sheehan Disability Scale (SDS), a three-item instrument for assessing psychiatric impairment in occupational, social and family functioning, each rated from 0 to 10 (0-3: mild impairment; 4-6: moderate impairment; 7-10: severe impairment). Internal consistency reliability was demonstrated with the coefficient alpha was 0.89 for three-item scale. Reliability of each item ranged from 0.67 for work impairment to 0.77 for family impairment and 0.81 for social impairment. The construct validity was proved as well (Leon, Olfson, Portera, Farber, & Sheehan, 1997).

Swanson, Kotlin, Agler, M-Flynn and Pelham (SKAMP) scale is a 15-item scale. Ten items describe typical behaviors in a classroom setting and other five items were used for recording specific behavior (Swanson, 1992). Items are rated on a 7-point impairment scale (none, slight, mild, moderate, severe, very severe, and maximal). The reliabilities were from .70 to .78 for the SKAMP Attention ratings, and were from .63 to .73 for the SKAMP Dependent ratings. The concurrent validity was established by calculating correlations with Conners and the IOWA Conners Rating scale (Wigal, Gupta, Guinta, & Swanson, 1998).

Wender Utah Rating Scale (WURS) is a 61-item scale for adults to evaluate childhood behavior. It has been demonstrated to be sensitive in identifying childhood attention deficit hyperactivity disorder. It is rated on the five-point scale: 'not at all or slightly', 'mildly', 'moderately', 'quite a bit', and 'very much'. A subset of 25 of the items successfully identified 86% of patients diagnosed with ADHD and 99% of the normal, control individuals (Ward, Wender, & Reimherr, 1993). The test-retest reliability was proved with Cronbach alpha ranged from .69 to .90. The validity was demonstrated as well with factor analysis (Rossini & O'Connor, 1995; Stein et al., 1995).

Wechsler Intelligence Scale for Children, 3rd edition (WISC-III) is an instrument assessing the intellectual ability of children aged 6 to 16 years. It consists of different measures to estimate

individual's intellectual abilities. Each subtest is derived from four factors, verbal comprehension, perceptual organization, freedom from distractibility and processing speed. The reliability coefficients of the subscales are from .69-.96. Besides, it has been demonstrated in construct validity and internal validity (Wechsler, 1991).

Werry-Quay Direct Observational System assesses behaviors including out-of-seat; physical contact or disturbing others; audible noise; ninety-degree turn, seated; inappropriate vocalizations; other deviant behaviors; and daydreaming. Retrieval of reliability and validity findings (Werry & Quay, 1969) are pending and will be addressed in the updated report.

References for Appendix A

1. Achenbach, T. M. (1999). The child behavior checklist and related instruments. In M. E. Maruish (Ed.), *The Use of Psychological Testing for Treatment Planning and Outcome Assessment* (2nd ed., pp. 429-465). Mahwah, NJ: Lawrence Erlbaum Associates.
2. Achenbach, T. M., & Edelbrock, C. S. (1981). Behavioral problems and competencies reported by parents of normal and disturbed children aged four through sixteen. *Monographs of the Society for Research in Child Development*, 46(1), 1-82.
3. Achenbach, T. M., & Edelbrock, C. S. (1983). *Manual for the Child Behavior Checklist and Revised Child Behavior Profile*. Burlington.
4. Atkins, M. S., Pelham, W. E., & Licht, M. H. (1989). The differential validity of teacher ratings of inattention/overactivity and aggression. *Journal of Abnormal Child Psychology*, 17(4), 423-435.
5. Barkley, R., & Murphy, K. (1998). *Attention-deficit hyperactivity disorder: a clinical workbook*. New York: Guilford Press.
6. Barratt, E. (1985). Impulsiveness subtraits: arousal and information processing. In *Motivation, Emotion, and Personality* (pp. 137-146). North-Holland: Elsevier Science Publishers B.V.
7. Brown, T. E. (1996). *Brown ADD Scale*. The Psychological Corporation. San Antonio, Texas: Harcourt Brace & Company.
8. Conners, C., Erhardt, D., & Sparrow, E. (1999). *Conner's Adult ADHD Rating Scales (CAARS): technical manual*. North Tonawanda: Multi-Health Systems (MHS), Inc.
9. Copeland, E. (1989). *Copeland Symptom Checklist for Adult Attention Deficit Disorders*. Atlanta: SPI Southeastern Psychological Institute.
10. Derogatis, L. R., Lipman, R. S., & Covi, L. (1973). SCL-90: an outpatient psychiatric rating scale--preliminary report. *Psychopharmacology Bulletin*, 9(1), 13-28.
11. Derogatis, L. R., Rickels, K., & Rock, A. F. (1976). The SCL-90 and the MMPI: a step in the validation of a new self-report scale. *British Journal of Psychiatry*, 128, 280-289.
12. DuPaul, G. J. (1998). *ADHD Rating Scale-IV: Checklists, Norms, and Clinical Interpretation*. New York, NY: Guilford Press.
13. Endicott, J., Spitzer, R. L., Fleiss, J. L., & Cohen, J. (1976). The global assessment scale. A procedure for measuring overall severity of psychiatric disturbance. *Archives of General Psychiatry*, 33(6), 766-771.
14. Epstein, J. N., Conners, C. K., Sitarenios, G., & Erhardt, D. (1998). Continuous performance test results of adults with attention deficit hyperactivity disorder. *Clinical Neuropsychologist*, 12(2), 155-168.

15. Goyette, C. H., Conners, C. K., & Ulrich, R. F. (1978). Normative data on revised Conners Parent and Teacher Rating Scales. *Journal of Abnormal Child Psychology*, 6(2), 221-236.
16. Guy, W. (1976). ECDEU assessment manual for psychopharmacology. In P. R. B. National Institute of Mental Health (U.S.), Division of Extramural Research Programs. (Ed.) (pp. 603). Rockville, Maryland: U.S. Dept. of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Program.
17. Halperin, J. M., Greenblatt, E., Sharma, V., & Schwartz, S. T. (1991). Assessment of the continuous performance test: reliability and validity in a nonreferred sample. *Psychological Assessment*, 3(4), 603-608.
18. Leon, A. C., Olfson, M., Portera, L., Farber, L., & Sheehan, D. V. (1997). Assessing psychiatric impairment in primary care with the Sheehan Disability Scale. *International Journal of Psychiatry in Medicine*, 27(2), 93-105.
19. Loney, J., & Milich, R. S. (1982). Hyperactivity, inattention, and aggression in clinical practice. In M. Wolraich & D. Routh (Eds.), *Advances in Development and Behavioral Pediatrics*, Vol. 3 (Vol. 3, pp. 113-147). Greenwich, CT: JAI Press.
20. Nuechterlein, K. H. (1983). Signal detection in vigilance tasks and behavioral attributes among offspring of schizophrenic mothers and among hyperactive children. *Journal of Abnormal Psychology*, 92(1), 4-28.
21. Rapoport, J. L., Buchsbaum, M. S., Weingartner, H., Zahn, T. P., Ludlow, C., & Mikkelsen, E. J. (1980). Dextroamphetamine. Its cognitive and behavioral effects in normal and hyperactive boys and normal men. *Archives of General Psychiatry*, 37(8), 933-943.
22. Rossini, E. D., & O'Connor, M. A. (1995). Retrospective self-reported symptoms of attention-deficit hyperactivity disorder: reliability of the Wender Utah Rating Scale. *Psychological Reports*, 77(3 Pt 1), 751-754.
23. Rosvold, H. E., Mirsky, A. F., Sarason, I., Bransome Jr, E. D., & Beck, L. H. (1956). A continuous performance test of brain damage. *Journal of Consulting Psychology*, 20(5), 343-350.
24. Shaffer, D., Gould, M. S., Brasic, J., Ambrosini, P., Fisher, P., Bird, H., et al. (1983). A children's global assessment scale (CGAS). *Archives of General Psychiatry*, 40(11), 1228-1231.
25. Stein, M. A., Sandoval, R., Szumowski, E., Roizen, N., Reinecke, M. A., Blondis, T. A., et al. (1995). Psychometric characteristics of the Wender Utah Rating Scale (WURS): reliability and factor structure for men and women. *Psychopharmacology Bulletin*, 31(2), 425-433.
26. Swanson, J. M. (1992). *School-based assessments and interventions for ADD students*. Irvine, CA: KC Publishing.
27. Ward, M. F., Wender, P. H., & Reimherr, F. W. (1993). The Wender Utah Rating Scale: an aid in the retrospective diagnosis of childhood attention deficit hyperactivity disorder.[erratum appears in Am J Psychiatry 1993 Aug;150(8):1280]. *American Journal of Psychiatry*, 150(6), 885-890.
28. Wechsler, D. (1991). *WISC-III [kit] : Wechsler intelligence scale for children* (3rd ed.). San Antonio, TX: Psychological Corporation, Harcourt Brace Jovanovich.

29. Wender, P. H., Reimherr, F. W., Wood, D., & Ward, M. (1985). A controlled study of methylphenidate in the treatment of attention deficit disorder, residual type, in adults. *American Journal of Psychiatry*, 142(5), 547-552.
30. Werry, J. S., & Quay, H. C. (1969). Observing the classroom behavior of elementary school children. *Exceptional Children*, 35, 461-470.
31. Wigal, S. B., Gupta, S., Guinta, D., & Swanson, J. M. (1998). Reliability and validity of the SKAMP rating scale in a laboratory school setting. *Psychopharmacology Bulletin*, 34(1), 47-53.

Appendix B. Search Strategies

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2005>

Search Strategy:

-
- 1 Methylphenidate.mp.
 - 2 concerta.mp.
 - 3 metadate.mp.
 - 4 methylin.mp.
 - 5 ritalin.mp.
 - 6 dexamethylphenidate.mp.
 - 7 focalin.mp.
 - 8 pemoline.mp.
 - 9 cylert.mp.
 - 10 amphetamine\$.mp.
 - 11 adderall.mp. (21)
 - 12 dextroamphetamine.mp.
 - 13 Dexedrine.mp.
 - 14 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
 - 15 Atomoxetine.mp.
 - 16 Strattera.mp.
 - 17 wellbutrin.mp.
 - 18 bupropion.mp.
 - 19 modafinil.mp.
 - 20 provigil.mp.
 - 21 clonidine.mp.
 - 22 catapres.mp.
 - 23 guanfacine.mp.
 - 24 tenex.mp.
 - 25 aripiprazole.mp.
 - 26 clozapine.mp.
 - 27 clozaril.mp.
 - 28 olanzapine.mp.
 - 29 zyprexa.mp.
 - 30 quetiapine.mp.
 - 31 seroquel.mp.
 - 32 risperidone.mp.
 - 33 risperdal.mp.
 - 34 ziprasidone.mp.
 - 35 geodon.mp.
 - 36 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
 - or 31 or 32 or 33 or 34 or 35
 - 37 Attention Deficit Disorder with Hyperactivity/
 - 38 attention deficit disorder/
 - 39 attention deficit.mp.
 - 40 adhd.mp.

- 41 37 or 38 or 39 or 40
- 42 14 or 36
- 43 41 and 42
- 44 from 43 keep 1-524

Database: Ovid MEDLINE(R) <1966 to October Week 1 2005>
Search Strategy:

- 1 Methylphenidate.mp.
- 2 concerta.mp.
- 3 metadate.mp.
- 4 methylin.mp.
- 5 ritalin.mp.
- 6 dexmethylphenidate.mp.
- 7 focalin.mp.
- 8 pemoline.mp.
- 9 cylert.mp.
- 10 amphetamine\$.mp.
- 11 adderall.mp.
- 12 dextroamphetamine.mp.
- 13 Dexedrine.mp.
- 14 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
- 15 Atomoxetine.mp.
- 16 Strattera.mp.
- 17 wellbutrin.mp.
- 18 bupropion.mp.
- 19 modafinil.mp.
- 20 provigil.mp.
- 21 clonidine.mp.
- 22 catapres.mp.
- 23 guanfacine.mp.
- 24 tenex.mp.
- 25 aripiprazole.mp.
- 26 clozapine.mp.
- 27 clozaril.mp.
- 28 olanzapine.mp.
- 29 zyprexa.mp.
- 30 quetiapine.mp.
- 31 seroquel.mp.
- 32 risperidone.mp.
- 33 risperdal.mp.
- 34 ziprasidone.mp.
- 35 geodon.mp.

36 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
 or 31 or 32 or 33 or 34 or 35
 37 Attention Deficit Disorder with Hyperactivity/
 38 attention deficit.mp.
 39 adhd.mp.
 40 37 or 38 or 39
 41 14 or 36
 42 40 and 41
 43 limit 42 to (controlled clinical trial or meta analysis or randomized controlled trial) (429)
 44 (systemat\$ adj5 review\$).mp.
 45 Randomized Controlled Trials/
 46 cohort\$.mp.
 47 44 or 45 or 46
 48 42 and 47
 49 43 or 48
 50 adverse effect\$.mp. or ae.fs.
 51 poisoning.mp. or po.fs.
 52 toxicity.mp. or to.fs.
 53 50 or 51 or 52
 54 41 and 53
 55 limit 54 to (controlled clinical trial or meta analysis or randomized controlled trial)
 56 47 and 54
 57 55 or 56
 58 49 or 57
 59 limit 58 to human
 60 limit 59 to english language
 61 limit 59 to abstracts
 62 60 or 61
 63 from 62 keep 1-1630

Database: PsycINFO <1974 to September Week 4 2005>

Search Strategy:

 1 Methylphenidate.mp.
 2 concerta.mp.
 3 metadate.mp.
 4 methylin.mp.
 5 ritalin.mp.
 6 dexmethylphenidate.mp.
 7 focalin.mp.
 8 pemoline.mp.
 9 cylert.mp.
 10 amphetamine\$.mp.
 11 adderall.mp.
 12 dextroamphetamine.mp.

13 Dexedrine.mp.
 14 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
 15 Atomoxetine.mp.
 16 Strattera.mp.
 17 wellbutrin.mp.
 18 bupropion.mp.
 19 modafinil.mp.
 20 provigil.mp.
 21 clonidine.mp.
 22 catapres.mp.
 23 guanfacine.mp.
 24 tenex.mp.
 25 aripiprazole.mp.
 26 clozapine.mp.
 27 clozaril.mp.
 28 olanzapine.mp.
 29 zyprexa.mp.
 30 quetiapine.mp.
 31 seroquel.mp.
 32 risperidone.mp.
 33 risperdal.mp.
 34 ziprasidone.mp.
 35 geodon.mp.
 36 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
 or 31 or 32 or 33 or 34 or 35
 37 Attention Deficit Disorder with Hyperactivity/
 38 attention deficit.mp.
 39 adhd.mp.
 40 37 or 38 or 39
 41 14 or 36
 42 40 and 41
 43 ((systemat\$ adj5 review\$) or meta-analysis).mp.
 44 (random\$ or double blind\$ or placebo\$.mp.
 45 controlled clinical trial\$.mp.
 46 cohort\$.mp.
 47 43 or 44 or 46
 48 42 and 47
 49 exp "Side Effects (Drug)"/ or exp Drug Interactions/ or adverse effect\$.mp.
 50 36 and 47 and 49
 51 48 or 50
 52 limit 51 to english language
 53 51 not 52
 54 limit 53 to abstracts
 55 52 or 54
 56 from 55 keep 1-740

.....

Embase

```
((('methylphenidate'/exp OR 'concerta'/exp OR metadata OR methylin OR 'ritalin'/exp OR  
'dexmethylphenidate'/exp OR 'focalin'/exp OR 'pemoline'/exp OR 'cylert'/exp OR amphetamine$  
OR 'adderall'/exp OR 'dextroamphetamine'/exp OR 'dexedrine'/exp AND [embase]/lim) OR  
('atomoxetine'/exp OR 'strattera'/exp OR 'wellbutrin'/exp OR 'bupropion'/exp OR 'modafinil'/exp  
OR 'provigil'/exp OR 'clonidine'/exp OR 'catapres'/exp OR 'guanfacine'/exp OR 'tenex'/exp OR  
'aripiprazole'/exp OR 'clozapine'/exp OR 'clozaril'/exp OR 'olanzapine'/exp OR 'zyprexa'/exp OR  
'quetiapine'/exp OR 'seroquel'/exp OR 'risperidone'/exp OR 'risperdal'/exp OR 'ziprasidone'/exp  
OR 'geodon'/exp AND [embase]/lim))  
AND  
('attention deficit disorder'/exp OR adhd OR 'attention deficit'/exp AND [embase]/lim))  
AND  
([meta analysis]/lim OR [randomized controlled trial]/lim)  
AND  
[embase]/lim
```

Appendix C. Quality assessment methods for drug class reviews for the Drug Effectiveness Review Project

The purpose of this document is to outline the methods used by the Oregon Evidence-based Practice Center (EPC), based at Oregon Health & Science University, and any subcontracting EPCs, in producing drug class reviews for the Drug Effectiveness Review Project.

The methods outlined in this document ensure that the products created in this process are methodologically sound, scientifically defensible, reproducible, and well documented. This document has been adapted from the Procedure Manual developed by the Methods Work Group of the United States Preventive Services Task Force (version 1.9, September 2001), with additional material from the NHS Centre for Reviews and Dissemination (CRD) report on *Undertaking Systematic Reviews of Research on Effectiveness: CRD's Guidance for Carrying Out or Commissioning Reviews* (2nd edition, 2001) and “The Database of Abstracts of Reviews of Effects (DARE)” in *Effectiveness Matters*, vol. 6, issue 2, December 2002, published by the CRD.

All studies or systematic reviews that are included are assessed for quality, and assigned a rating of “good”, “fair” or “poor”. Studies that have a fatal flaw in one or more criteria are rated poor quality; studies which meet all criteria, are rated good quality; the remainder are rated fair quality. As the “fair quality” category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair quality studies are *likely* to be valid, while others are only *probably* valid. A “poor quality” trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs.

For Controlled Trials:

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?

Adequate approaches to sequence generation:

Computer-generated random numbers

Random numbers tables

Inferior approaches to sequence generation:

Use of alternation, case record numbers, birth dates or week days

Not reported

2. Was the treatment allocation concealed?

Adequate approaches to concealment of randomization:

Centralized or pharmacy-controlled randomization

Serially-numbered identical containers

On-site computer based system with a randomization sequence that is not readable until allocation

Other approaches sequence to clinicians and patients

Inferior approaches to concealment of randomization:

Use of alternation, case record numbers, birth dates or week days

Open random numbers lists

Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)

Not reported

3. Were the groups similar at baseline in terms of prognostic factors?
4. Were the eligibility criteria specified?
5. Were outcome assessors blinded to the treatment allocation?
6. Was the care provider blinded?
7. Was the patient kept unaware of the treatment received?
8. Did the article include an intention-to-treat analysis, or provide the data needed to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?
9. Did the study maintain comparable groups?
10. Did the article report attrition, crossovers, adherence, and contamination?
11. Is there important differential loss to followup or overall high loss to followup? (give numbers in each group)

Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom the intervention would be applied?
2. How many patients were recruited?
3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)
4. What was the funding source and role of funder in the study?
5. Did the control group receive the standard of care?
6. What was the length of followup? (Give numbers at each stage of attrition.)

For Studies Reporting Complications/Adverse EffectsAssessment of Internal Validity

1. Was the selection of patients for inclusion non-biased (Was any group of patients systematically excluded)?

2. Is there important differential loss to followup or overall high loss to followup? (Give numbers in each group.)

3. Were the events investigated specified and defined?

4. Was there a clear description of the techniques used to identify the events?

5. Was there non-biased and accurate ascertainment of events (independent ascertainers; validation of ascertainment technique)?

6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?

7. Did the duration of followup correlate to reasonable timing for investigated events? (Does it meet the stated threshold?)

Assessment of External Validity

1. Was the description of the population adequate?

2. How similar is the population to the population to whom the intervention would be applied?

3. How many patients were recruited?

4. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

5. What was the funding source and role of funder in the study?

Systematic Reviews:

1. Is there a clear review question and inclusion/exclusion criteria reported relating to the primary studies?

A good quality review should focus on a well-defined question or set of questions, which ideally will refer to the inclusion/exclusion criteria by which decisions are made on whether to include or exclude primary studies. The criteria should relate to the four components of study design, indications (patient populations), interventions (drugs), and outcomes of

interest. In addition, details should be reported relating to the process of decision-making, i.e., how many reviewers were involved, whether the studies were examined independently, and how disagreements between reviewers were resolved.

2. Is there evidence of a substantial effort to search for all relevant research?

This is usually the case if details of electronic database searches and other identification strategies are given. Ideally, details of the search terms used, date and language restrictions should be presented. In addition, descriptions of hand-searching, attempts to identify unpublished material, and any contact with authors, industry, and research institutes should be provided. The appropriateness of the database(s) searched by the authors should also be considered, e.g. if MEDLINE is searched for a review looking at health education, then it is unlikely that all relevant studies will have been located.

3. Is the validity of included studies adequately assessed?

A systematic assessment of the quality of primary studies should include an explanation of the criteria used (e.g., method of randomization, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis). Authors may use either a published checklist or scale, or one that they have designed specifically for their review. Again, the process relating to the assessment should be explained (i.e. how many reviewers involved, whether the assessment was independent, and how discrepancies between reviewers were resolved).

4. Is sufficient detail of the individual studies presented?

The review should demonstrate that the studies included are suitable to answer the question posed and that a judgement on the appropriateness of the authors' conclusions can be made. If a paper includes a table giving information on the design and results of the individual studies, or includes a narrative description of the studies within the text, this criterion is usually fulfilled. If relevant, the tables or text should include information on study design, sample size in each study group, patient characteristics, description of interventions, settings, outcome measures, follow-up, drop-out rate (withdrawals), effectiveness results and adverse events.

5. Are the primary studies summarized appropriately?

The authors should attempt to synthesize the results from individual studies. In all cases, there should be a narrative summary of results, which may or may not be accompanied by a quantitative summary (meta-analysis).

For reviews that use a meta-analysis, heterogeneity between studies should be assessed using statistical techniques. If heterogeneity is present, the possible reasons (including chance) should be investigated. In addition, the individual evaluations should be weighted in some way (e.g., according to sample size, or inverse of the variance) so that studies that are considered to provide the most reliable data have greater impact on the summary statistic.

Appendix D. Study citations identified through public comment process

Published After Search Dates for Update 1

1. Allen AJ, Kurlan RM, Gilbert DL, et al. Atomoxetine treatment in children and adolescents with ADHD and comorbid tic disorders. *Neurology*. 2005;65(12):1941-1949.
2. Biederman J, Spencer TJ, Wilens TE, et al. Long-term safety and effectiveness of mixed amphetamine salts extended release in adults with ADHD. *Cns Spectrums*. 2005;10(12 Suppl 20):16-25.
3. Biederman J, Wigal S, Spencer T, McGough J, Mays D. A posthoc subgroup analysis of an 18-day randomized controlled trial comparing the tolerability and efficacy of mixed amphetamine salts extended release and atomoxetine in school-aged girls with attention-deficit/hyperactivity disorder. *Clinical Therapeutics*. 2006;28(2):280-293.
4. Goodman DW, Ginsberg L, Weisler RH, Cutler AJ, Hodgkins P. An interim analysis of the Quality of Life, Effectiveness, Safety, and Tolerability (Q.U.E.S.T.) evaluation of mixed amphetamine salts extended release in adults with ADHD. *Cns Spectrums*. 2005;10(12 Suppl 20):26-34.
5. Hazell P, Zhang S, Wolanczyk T, et al. Comorbid oppositional defiant disorder and the risk of relapse during 9 months of atomoxetine treatment for ADHD. *European Child & Adolescent Psychiatry*. 2006;15(2):105-110.
6. Kessler RC, Adler L, Barkley RA, et al. The prevalence and correlates of adult ADHD in the United States: results from the national comorbidity survey replication. *American Journal of Psychiatry*. 2006;163:716-723.
7. Spencer T, Wilens T, Biederman J, Weisler RH, Read SC, Pratt R. Efficacy and safety of mixed amphetamine salts extended release (Adderall XR) in the management of attention deficit/hyperactivity disorder in adolescent patients: a 4-week, randomized, double-blind, placebo-controlled, parallel-group study. *Clinical Therapeutics*. 2006;28(2):266-279.
8. Weisler RH, Biederman J, Spencer TJ, Wilens TE. Long-term cardiovascular effects of mixed amphetamine salts extended release in adults with ADHD. *Cns Spectrums*. 2005;10(12 Suppl 20):35-43.
9. Wilens TE, Kratochvil C, Newcorn JH, Gao H. Do children and adolescents with ADHD respond differently to atomoxetine? *Journal of the American Academy of Child & Adolescent Psychiatry*. 2006;45(2):149-157.

Studies Currently Under Review / In-Process

1. Adler LA, Spencer TJ, Milton DR, Moore RJ, Michelson D. Long-term, open-label study of the safety and efficacy of atomoxetine in adults with attention-deficit/hyperactivity disorder: an interim analysis. *Journal of Clinical Psychiatry*. 2005;66(3):294-299.
2. American Academy of Child and Adolescent Psychiatry. *Guidelines Pocketbook(R) Managing: Attention-Deficit Hyperactivity Disorder, Version 2*. Baltimore, MD: International Guidelines Center; 2004.
3. Barkley. *Attention-deficit hyperactivity disorder: a handbook for diagnosis and treatment*. New York, NY: The Guildford Press; 1998.
4. Connor D, Spencer T. Short-term cardiovascular effects of mixed amphetamine salts

- extended release in children and adolescents with oppositional defiant disorder. *Cns Spectrums*. 2005;10(Suppl 15):31-38.
5. Faraone SV, Biederman J, Monuteaux M, Spencer T. Long-term effects of extended-release mixed amphetamine salts treatment of attention-deficit/hyperactivity disorder on growth. *Journal of Child & Adolescent Psychopharmacology*. 2005;15(2):191-202.
 6. Faraone SV, Biederman J, Spencer T, et al. Atomoxetine and stroop task performance in adult attention-deficit/hyperactivity disorder. *Journal of Child & Adolescent Psychopharmacology*. 2005;15(4):664-670.
 7. Findling RL, Biederman J, Wilens TE, et al. Short- and long-term cardiovascular effects of mixed amphetamine salts extended release in children.[see comment]. *Journal of Pediatrics*. 2005;147(3):348-354.
 8. Newcorn JH, Spencer TJ, Biederman J, Milton DR, Michelson D. Atomoxetine treatment in children and adolescents with attention-deficit/hyperactivity disorder and comorbid oppositional defiant disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2005;44(3):240-248.
 9. Reimherr FW, Marchant BK, Strong RE, et al. Emotional Dysregulation in Adult ADHD and Response to Atomoxetine. *Biological psychiatry*. Jul 2005;58(2):125-131.
 10. Spencer T, Biederman J, Wilens T. Efficacy and tolerability of long-term, open-label, mixed amphetamine salts extended release in adolescents with ADHD. *Cns Spectrums*. 2005;10(Suppl 15):14-21.
 11. Swanson J, Gupta S, Lam A, et al. Development of a new once-a-day formulation of methylphenidate for the treatment of attention-deficit/hyperactivity disorder: proof-of-concept and proof-of-product studies. *Archives of General Psychiatry*. 2003;60(2):204-211.
 12. Swanson J, McBurnett K, Wigal T, al. e. Effect of stimulant medication on children with attention-deficit disorder - a review of reviews. *Exceptional Children*. 1993;60:154-162.
 13. Thurber S. Medications and hyperactivity. A meta-analysis. *Journal of General Psychology*. 1983;108:79-86.
 14. Wilens T, McBurnett K, Stein M, Lerner M, Spencer T, Wolraich M. ADHD treatment with once-daily OROS methylphenidate: final results from a long-term open-label study. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2005;44(10):1015-1023.
 15. Wilens T, Spencer T, Biederman J. Short- and long-term cardiovascular effects of mixed amphetamine salts extended release in adolescents with ADHD. *Cns Spectrums*. 2005;10(Suppl 15):22-30.

Studies that were poster presentations or abstract only were excluded.

Appendix E. Excluded Studies

1. Aarskog D, Fevang FO, Klove H, Stoa KF, Thorsen T. The effect of the stimulant drugs, dextroamphetamine and methylphenidate, on secretion of growth hormone in hyperactive children. *Journal of Pediatrics*. 1977;90(1):136-139.
2. Abramowitz AJ, Eckstrand D, O'Leary SG, Dulcan MK. ADHD children's responses to stimulant medication and two intensities of a behavioral intervention. *Behavior Modification*. Apr 1992;16(2):193-203.
3. Adams W. Effect of methylphenidate on thought processing time in children. *Journal of Developmental & Behavioral Pediatrics*. 1982;3(3):133-135.
4. Ahmann PA, Theye FW, Berg R, et al. Long-term behavioral response to adderall in children and adolescents with ADHD. *Pediatric Research*. 2000;47(4):22A.
5. Ahmann PA, Theye FW, Berg R, Linquist AJ, Van Erem AJ, Campbell LR. Placebo-controlled evaluation of amphetamine mixture-dextroamphetamine salts and amphetamine salts (Adderall): efficacy rate and side effects. *Pediatrics*. 2001;107(1):168.
6. Ajibola O, Clement PW. Differential effects of methylphenidate and self-reinforcement on attention-deficit hyperactivity disorder. *Behavior Modification*. 1995;19(2):211-233.
7. Aman MG, Binder C, Turgay A. Risperidone effects in the presence/absence of psychostimulant medicine in children with ADHD, other disruptive behavior disorders, and subaverage IQ. *Journal of Child & Adolescent Psychopharmacology*. 2004;14(2):243-254.
8. Aman MG, Buican B, Arnold L. Methylphenidate treatment in children with borderline IQ and mental retardation: Analysis of three aggregated studies. *Journal of Child & Adolescent Psychopharmacology*. Spr 2003;13(1):29-40.
9. Aman MG, Kern RA, McGhee DE, Arnold LE. Fenfluramine and methylphenidate in children with mental retardation and ADHD: clinical and side effects. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1993;32(4):851-859.
10. Aman MG, Kern RA, McGhee DE, Arnold LE. Fenfluramine and methylphenidate in children with mental retardation and attention deficit hyperactivity disorder: laboratory effects. *Journal of Autism & Developmental Disorders*. 1993;23(3):491-506.
11. Aman MG, Kern RA, Osborne P, Tumulu R, Rojahn J, del Medico V. Fenfluramine and methylphenidate in children with mental retardation and borderline IQ: clinical effects. *American Journal of Mental Retardation*. 1997;101(5):521-534.
12. Aman MG, Marks RE, Turbott SH, Wilsher CP, Merry SN. Clinical effects of methylphenidate and thioridazine in intellectually subaverage children. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1991;30(2):246-256.
13. Aman MG, Marks RE, Turbott SH, Wilsher CP, Merry SN. Methylphenidate and thioridazine in the treatment of intellectually subaverage children: effects on cognitive-motor performance. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1991;30(5):816-824.
14. Ambrosini PJ, Sallee F, Lopez F, Shi L, Michaels MA, Group LCS. A community assessment, open-label study of the safety, tolerability, and effectiveness of mixed amphetamine salts extended release in school-aged children with ADHD. *Current Medical Research & Opinion*. Feb 2006;22(2):427-440.
15. Amery B, Minichiello MD, Brown GL. Aggression in hyperactive boys: Response to d-

- amphetamine. *Journal of the American Academy of Child Psychiatry*. May 1984;23(3):291-294.
16. Anderson EE, Clement PW, Oettinger L, Jr. Methylphenidate compared with behavioral self-control in attention deficit disorder: preliminary report. *Journal of Developmental & Behavioral Pediatrics*. 1981;2(4):137-141.
 17. Arnett PA, et al. The Effect of Ritalin on Response to Reward and Punishment in Children with ADHD. *Child Study Journal*. 1996;26(1):51-70.
 18. Arnett PA, et al. The Effect of Ritalin on Response to Reward and Punishment in Children with ADHD. *Child-Study-Journal*. 1996;26(1):51-70.
 19. Arnold LE, Abikoff HB, Cantwell DP, et al. National Institute of Mental Health Collaborative Multimodal Treatment Study of Children with ADHD (the MTA). Design challenges and choices. *Archives of General Psychiatry*. 1997;54(9):865-870.
 20. Arnold LE, Huestis RD, Smeltzer DJ, Scheib J, Wemmer D, Colner G. Levoamphetamine vs dextroamphetamine in minimal brain dysfunction. Replication, time response, and differential effect by diagnostic group and family rating. *Archives of General Psychiatry*. 1976;33(3):292-301.
 21. Arnold LE, Kleykamp D, Votolato NA, Taylor WA, Kontras SB, Tobin K. Gamma-linolenic acid for attention-deficit hyperactivity disorder: placebo-controlled comparison to D-amphetamine. *Biological Psychiatry*. 1989;25(2):222-228.
 22. Arnold LE, Wender PH, McCloskey K, Snyder SH. Levoamphetamine and dextroamphetamine: comparative efficacy in the hyperkinetic syndrome. *Archives of General Psychiatry*. 1972;27(6):816-822.
 23. Ballinger CT, Varley CK, Nolen PA. Effects of methylphenidate on reading in children with attention deficit disorder. *American Journal of Psychiatry*. 1984;141(12):1590-1593.
 24. Balthazor MJ, Wagner RK, Pelham WE. The specificity of the effects of stimulant medication on classroom learning-related measures of cognitive processing for attention deficit disorder children. *Journal of Abnormal Child Psychology*. 1991;19(1):35-52.
 25. Barkley RA, DuPaul GJ, McMurray MB. Attention deficit disorder with and without hyperactivity: clinical response to three dose levels of methylphenidate. *Pediatrics*. 1991;87(4):519-531.
 26. Barkley RA, Fischer M, Newby RF, Breen MJ. Development of a multimethod clinical protocol for assessing stimulant drug response in children with attention deficit disorder. *Journal of Clinical Child Psychology*. Mar 1988;17(1):14-24.
 27. Barkley RA, Karlsson J, Pollard S, Murphy JV. Developmental changes in the mother-child interactions of hyperactive boys: effects of two dose levels of Ritalin. *Journal of Child Psychology & Psychiatry & Allied Disciplines*. 1985;26(5):705-715.
 28. Barkley RA, Karlsson J, Strzelecki E, Murphy JV. Effects of age and Ritalin dosage on the mother-child interactions of hyperactive children. 1984;No. 5:750-758. Located at: *Journal of Consulting & Clinical Psychology*.
 29. Barkley RA, McMurray MB, Edelbrock CS, Robbins K. The response of aggressive and nonaggressive ADHD children to two doses of methylphenidate [published erratum appears in J Am Acad Child Adolesc Psychiatry 1990 Jul; 29 (4) 670]. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1989;28(6):873-881.
 30. Barkley RA, McMurray MB, Edelbrock CS, Robbins K. Side effects of methylphenidate

- in children with attention deficit hyperactivity disorder: a systemic, placebo-controlled evaluation. *Pediatrics*. 1990;86(2):184-192.
31. Becker-Mattes A, Mattes JA, Abikoff H, Brandt L. State-dependent learning in hyperactive children receiving methylphenidate. *American Journal of Psychiatry*. Apr 1985;142(4):455-459.
 32. Bedard AC, Ickowicz A, Logan GD, Hogg-Johnson S, Schachar R, Tannock R. Selective inhibition in children with attention-deficit hyperactivity disorder off and on stimulant medication. *Journal of Abnormal Child Psychology*. 2003;31(3):315-327.
 33. Bedard AC, Ickowicz A, Tannock R. Methylphenidate improves Stroop naming speed, but not response interference, in children with attention deficit hyperactivity disorder. *Journal of Child & Adolescent Psychopharmacology*. 2002;12(4):301-309.
 34. Bedard AC, Martinussen R, Ickowicz A, Tannock R. Methylphenidate improves visual-spatial memory in children with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2004;43(3):260-268.
 35. Benedetto-Nasho E, Tannock R. Math computation, error patterns and stimulant effects in children with Attention Deficit Hyperactivity Disorder. *Journal of Attention Disorders*. Oct 1999;3(3):121-134.
 36. Berman T, Douglas VI, Barr RG. Effects of methylphenidate on complex cognitive processing in attention-deficit hyperactivity disorder. *Journal of Abnormal Psychology*. 1999;108(1):90-105.
 37. Biederman J, Lopez FA, Boellner SW, Chandler MC. A randomized, double-blind, placebo-controlled, parallel-group study of SLI381 (Adderall XR) in children with attention-deficit/hyperactivity disorder. *Pediatrics*. 2002;110(2 Pt 1):258-266.
 38. Biederman J, Quinn D, Weiss M, et al. Efficacy and safety of Ritalin LA, a new, once daily, extended-release dosage form of methylphenidate, in children with attention deficit hyperactivity disorder. *Pediatric Drugs*. 2003;5(12):833-841.
 39. Biederman J, Wilens T, Mick E, Spencer T, Faraone SV. Pharmacotherapy of attention-deficit/hyperactivity disorder reduces risk for substance use disorder. *Pediatrics*. 1999;104(2).
 40. Borcharding BG, Keysor CS, Cooper TB, Rapoport JL. Differential effects of methylphenidate and dextroamphetamine on the motor activity level of hyperactive children. *Neuropsychopharmacology*. 1989;2(4):255-263.
 41. Brown RT, Borden KA, Clingerman SR. Adherence to methylphenidate therapy in a pediatric population: a preliminary investigation. *Psychopharmacology Bulletin*. 1985;21(1):28-36.
 42. Brown RT, Borden KA, Spunt AL, Medenis R. Depression following pemoline withdrawal in a hyperactive child. *Clinical Pediatrics*. Mar 1985;24(3):174.
 43. Brown RT, Borden KA, Wynne ME, Spunt AL, Clingerman SR. Compliance with pharmacological and cognitive treatments for attention deficit disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1987;26(4):521-526.
 44. Brown RT, Borden KA, Wynne ME, Spunt AL, Clingerman SR. Patterns of compliance in a treatment program for children with attention deficit disorder. *Journal of Compliance in Health Care*. 1988;3(1):23-39.
 45. Brown RT, Jaffe SL, Silverstein J, Magee H. Methylphenidate and hospitalized adolescents with conduct disorder: Dose effects on classroom behavior, academic performance, and impulsivity. *Journal of Youth & Adolescence*. Oct 1991;20(5):501-

- 518.
46. Brown RT, Sexson SB. Effects of methylphenidate on cardiovascular responses in attention deficit hyperactivity disordered adolescents. *Journal of Adolescent Health Care*. 1989;10(3):179-183.
 47. Brown RT, Wynne ME, Borden KA, Clingerman SR, Geniesse R, Spunt AL. Methylphenidate and cognitive therapy in children with attention deficit disorder: a double-blind trial. *Journal of Developmental & Behavioral Pediatrics*. 1986;7(3):163-174.
 48. Buhrmester D, Whalen CK, Henker B, MacDonald V, Hinshaw SP. Prosocial behavior in hyperactive boys: effects of stimulant medication and comparison with normal boys. *Journal of Abnormal Child Psychology*. 1992;20(1):103-121.
 49. Buitelaar JK, Danckaerts M, Gillberg C, et al. A prospective, multicenter, open-label assessment of atomoxetine in non-North American children and adolescents with ADHD. *European Child & Adolescent Psychiatry*. 2004;13(4):249-257.
 50. Buitelaar JK, Van der Gaag RJ, Swaab-Barneveld H, Kuiper M. Prediction of clinical response to methylphenidate in children with attention-deficit hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1995;34(8):1025-1032.
 51. Bukstein OG, Kolko DJ. Effects of methylphenidate on aggressive urban children with attention deficit hyperactivity disorder. *Journal of Clinical Child Psychology*. 1998;27(3):340-351.
 52. Bussing R, Zima BT, Mason D, Hou W, Garvan CW, Forness S. Use and persistence of pharmacotherapy for elementary school students with attention-deficit/hyperactivity disorder. *Journal of Child & Adolescent Psychopharmacology*. 2005;15(1):78-87.
 53. Butter HJ, Lapierre Y, Firestone P, Blank A. A comparative study of the efficacy of ACTH4-9 analog, methylphenidate, and placebo on attention deficit disorder with hyperkinesia. *Journal of Clinical Psychopharmacology*. 1983;3(4):226-230.
 54. Butter HJ, Lapierre Y, Firestone P, Blank A. Efficacy of ACTH 4-9 analog, methylphenidate, and placebo on attention deficit disorder with hyperkinesia. *Progress in Neuro Psychopharmacology & Biological Psychiatry*. 1984;8(4-6):661-664.
 55. Campbell L, Malone MA, Kershner JR, Roberts W, Humphries T, Logan WJ. Methylphenidate slows right hemisphere processing in children with attention-deficit/hyperactivity disorder. *Journal of Child & Adolescent Psychopharmacology*. 1996;6(4):229-239.
 56. Carlson, Caryn L, Pelham, et al. ADHD boys' performance and attributions following success and failure: Drug effects and individual differences. *Cognitive Therapy & Research*. 1993;17(3):269-287.
 57. Carlson CL, Pelham W, Milich R, Dixon J. Single and combined effects of methylphenidate and behavior therapy on the classroom performance of children with attention-deficit hyperactivity disorder. *Journal of Abnormal Child Psychology*. 1992;20(2):213-232.
 58. Carlson CL, Pelham WE, Jr., Swanson JM, Wagner JL. A divided attention analysis of the effects of methylphenidate on the arithmetic performance of children with attention-deficit hyperactivity disorder. *Journal of Child Psychology & Psychiatry & Allied Disciplines*. 1991;32(3):463-471.
 59. Caro JJ, Ward A, Levinton C, Robinson K. The risk of diabetes during olanzapine use

- compared with risperidone use: a retrospective database analysis. *Journal of Clinical Psychiatry*. 2002;63(12):1135-1139.
60. Casat CD, Pearson DA, Van Davelaar MJ, Cherek DR. Methylphenidate effects on a laboratory aggression measure in children with ADHD. *Psychopharmacology Bulletin*. 1995;31(2):353-356.
 61. Castaneda R, Sussman N, Levy R, Trujillo M. A treatment algorithm for attention deficit hyperactivity disorder in cocaine-dependent adults: A one-year private practice study with long-acting stimulants, fluoxetine, and bupropion. *Substance Abuse*. Mar 1999;20(1):59-71.
 62. Charach A, Ickowicz A, Schachar R. Stimulant treatment over five years: adherence, effectiveness, and adverse effects. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2004;43(5):559-567.
 63. Chase SN, Clement PW. Effects of self-reinforcement and stimulants on academic performance in children with Attention Deficit Disorder. *Journal of Clinical Child Psychology*. Win 1985;14(4):323-333.
 64. Chatoor I, Wells KC, Conners CK, et al. The effects of nocturnally administered stimulant medication on EEG sleep and behavior in hyperactive children. *J Am Acad Child Psychiatr*. 1983;22(4):337-342.
 65. Clark E, Baker BK, Gardner MK, Pompa JL, et al. Effectiveness of stimulant drug treatment for attention problems: A look at head-injured children. *School Psychology International*. Aug 1990;11(3):227-234.
 66. Cook JR, Mausbach T, Burd L, et al. A preliminary study of the relationship between central auditory processing disorder and attention deficit disorder. *Journal of Psychiatry & Neuroscience*. 1993;18(3):130-137.
 67. Cotton MF, Rothberg AD. Methylphenidate v. placebo--a randomised double-blind crossover study in children with the attention deficit disorder. *South African Medical Journal*. 1988;74(6):268-271.
 68. Cox. The relative benefits of OROS® MPH vs seAMPHER in driving safety of teenagers with ADHD. Paper presented at: Pediatric Academic Societies Annual Meeting; May 14-17, 2005; Washington, DC.
 69. Cunningham CE, Siegel LS, Offord DR. A developmental dose-response analysis of the effects of methylphenidate on the peer interactions of attention deficit disordered boys. *Journal of Child Psychology & Psychiatry & Allied Disciplines*. 1985;26(6):955-971.
 70. Daviss WB, Bentivoglio P, Racusin R, Brown KM, Bostic JQ, Wiley L. Bupropion sustained release in adolescents with comorbid attention-deficit/hyperactivity disorder and depression. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2001;40(3):307-314.
 71. de Sonnevile LM, Njiokiktjien C, Bos H. Methylphenidate and information processing. Part 1: Differentiation between responders and nonresponders; Part 2: Efficacy in responders. *Journal of Clinical & Experimental Neuropsychology*. 1994;16(6):877-897.
 72. de Sonnevile LM, Njiokiktjien C, Hilhorst RC. Methylphenidate-induced changes in ADHD information processors. *Journal of Child Psychology & Psychiatry & Allied Disciplines*. 1991;32(2):285-295.
 73. Dewan MJ, Anand VS. Evaluating the tolerability of the newer antidepressants. *Journal of Nervous & Mental Disease*. Feb 1999;187(2):96-101.

74. Diamond IR, Tannock R, Schachar RJ. Response to methylphenidate in children with ADHD and comorbid anxiety. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1999;38(4):402-409.
75. DiTraglia J. Methylphenidate protocol: feasibility in a pediatric practice.[comment]. *Clinical Pediatrics*. 1991;30(12):656-660.
76. Donnelly M, Rapoport JL, Potter WZ, Oliver J, Keysor CS, Murphy DL. Fenfluramine and dextroamphetamine treatment of childhood hyperactivity. Clinical and biochemical findings. *Archives of General Psychiatry*. 1989;46(3):205-212.
77. Dorrego MF, Canevaro L, Kuzis G, Sabe L, Starkstein SE. A randomized, double-blind, crossover study of methylphenidate and lithium in adults with attention-deficit/hyperactivity disorder: preliminary findings. *Journal of Neuropsychiatry & Clinical Neurosciences*. 2002;14(3):289-295.
78. Douglas VI, Barr RG, O'Neill ME, Britton BG. Short term effects of methylphenidate on the cognitive, learning and academic performance of children with attention deficit disorder in the laboratory and the classroom. *Journal of Child Psychology & Psychiatry & Allied Disciplines*. 1986;27(2):191-211.
79. Downey KK, Sclrubiner H, Schuster CR. Double-blind placebo controlled stimulant trial for cocaine dependent adhd adults. *NIDA Research Monograph. Vol.* 2000;180:116.
80. Duggan CM, Mitchell G, Nikles CJ, Glasziou PP, Del Mar CB, Clavarino A. Managing ADHD in general practice. N of 1 trials can help! *Australian Family Physician*. 2000;29(12):1205-1209.
81. DuPaul GJ, Anastopoulos AD, Kwasnik D, Barkley RA, McMurray MB. Methylphenidate effects on children with attention deficit hyperactivity disorder: Self-report of symptoms, side-effects, and self-esteem. *Journal of Attention Disorders*. Apr 1996;1(1):3-15.
82. DuPaul GJ, Barkley RA, McMurray MB. Response of children with ADHD to methylphenidate: interaction with internalizing symptoms. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1994;33(6):894-903.
83. DuPaul GJ, Rapport MD. Does methylphenidate normalize the classroom performance of children with attention deficit disorder? *Journal of the American Academy of Child & Adolescent Psychiatry*. 1993;32(1):190-198.
84. DuPaul GJ, Rapport MD, Vyse SA. ADDH and methylphenidate responders: effects on behavior controlled by complex reinforcement schedules. *International Clinical Psychopharmacology*. 1988;3(4):349-361.
85. Dykman RA, Ackerman PT, McCray DS. Effects of methylphenidate on selective and sustained attention in hyperactive, reading-disabled, and presumably attention-disordered boys. *Journal of Nervous & Mental Disease*. 1980;168(12):745-752.
86. Efron D, Jarman F, Barker M. Methylphenidate versus dexamphetamine in children with attention deficit hyperactivity disorder: A double-blind, crossover trial. *Pediatrics*. 1997c;100(6):1025.
87. Efron D, Jarman FC, Barker MJ. Medium-term outcomes are comparable with short-term outcomes in children with attention deficit hyperactivity disorder treated with stimulant medication. *Journal of Paediatrics & Child Health*. 2000;36(5):457-461.
88. Eisenberg L. The hyperkinetic child and stimulant drugs. *New England Journal of Medicine*. 1972;287:249-250.
89. Elia J, Gulotta C, Rose SR, Marin G, Rapoport JL. Thyroid function and attention-deficit

- hyperactivity disorder.[comment]. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1994;33(2):169-172.
90. Evans RW, Gualtieri CT, Amara I. Methylphenidate and memory: dissociated effects in hyperactive children. *Psychopharmacology*. 1986;90(2):211-216.
 91. Evans SW, Pelham WE. Psychostimulant effects on academic and behavioral measures for ADHD junior high school students in a lecture format classroom. *Journal of Abnormal Child Psychology*. 1991;19(5):537-552.
 92. Feldman H, Crumrine P, Handen BL, Alvin R, Teodori J. Methylphenidate in children with seizures and attention-deficit disorder. *American Journal of Diseases of Children*. 1989;143(9):1081-1086.
 93. Findling RL, Short EJ, Manos MJ. Developmental aspects of psychostimulant treatment in children and adolescents with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2001;40(12):1441-1447.
 94. Findling RL, Short EJ, Manos MJ. Developmental aspects of psychostimulant treatment in children and adolescents with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2001a;40(12):1441-1447.
 95. Fine S, Jewesson B. Active drug placebo trial of methylphenidate--a clinical service for children with an attention deficit disorder. *Canadian Journal of Psychiatry Revue Canadienne de Psychiatrie*. 1989;34(5):447-449.
 96. Fine S, Johnston C. Drug and placebo side effects in methylphenidate-placebo trial for attention deficit hyperactivity disorder. *Child Psychiatry & Human Development*. 1993;24(1):25-30.
 97. Fischer M, Newby RF. Use of the Restricted Academic Task in ADHD dose-response relationships. *Journal of Learning Disabilities*. Nov 1998;31(6):608-612.
 98. Flintoff MM, Barron RW, Swanson JM, Ledlow A, Kinsbourne M. Methylphenidate increases selectivity of visual scanning in children referred for hyperactivity. *Journal of Abnormal Child Psychology*. 1982;10(2):145-161.
 99. Forness SR, Cantwell DP, Swanson JM, Hanna GL, Youpa D. Differential effects of stimulant medication on reading performance of boys with hyperactivity with and without conduct disorder. *Journal of Learning Disabilities*. 1991;24(5):304-310.
 100. Forness SR, Swanson JM, Cantwell D, Guthrie D, Sena R. Response to stimulant medication across six measures of school-related performance in children with ADHD and disruptive behavior. *Behavioral Disorders*. Nov 1992;18(1):42-53.
 101. Forness SR, Swanson JM, Cantwell DP, Youpa D, Hanna GL. Stimulant medication and reading performance: follow-up on sustained dose in ADHD boys with and without conduct disorders. *Journal of Learning Disabilities*. 1992;25(2):115-123.
 102. Francis S, Fine J, Tannock R. Methylphenidate selectively improves story retelling in children with attention deficit hyperactivity disorder. *Journal of Child & Adolescent Psychopharmacology*. 2001;11(3):217-228.
 103. Fredericks EM, Kollins SH. Assessing methylphenidate preference in ADHD patients using a choice procedure. *Psychopharmacology*. 2004;175(4):391-398.
 104. Gadow KD, Nolan EE, Sverd J, Sprafkin J, Paolicelli L. Methylphenidate in aggressive-hyperactive boys: I. Effects on peer aggression in public school settings. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1990;29(5):710-718.
 105. Gadow KD, Nolan EE, Sverd J, Sprafkin J, Schwartz J. Anxiety and depression symptoms and response to methylphenidate in children with attention-deficit

- hyperactivity disorder and tic disorder. *Journal of Clinical Psychopharmacology*. 2002;22(3):267-274.
106. Gadow KD, Sverd J, Sprafkin J, Nolan EE, et al. "Efficacy of methylphenidate for attention-deficit hyperactivity disorder in children with tic disorder": Correction. *Archives of General Psychiatry*. Oct 1995;52(10):836.
107. Gadow KD, Sverd J, Sprafkin J, Nolan EE, et al. Efficacy of methylphenidate for attention-deficit hyperactivity disorder in children with tic disorder. *Annual Progress in Child Psychiatry & Child Development*. 1996:494-522.
108. Gadow KD, Sverd J, Sprafkin J, Nolan EE, Ezor SN. Efficacy of methylphenidate for attention-deficit hyperactivity disorder in children with tic disorder. *Archives of General Psychiatry*. 1995;52(6):444-455.
109. Galanter CA, Carlson GA, Jensen PS, et al. Response to methylphenidate in children with attention deficit hyperactivity disorder and manic symptoms in the multimodal treatment study of children with attention deficit hyperactivity disorder titration trial. *Journal of Child & Adolescent Psychopharmacology*. 2003;13(2):123-136.
110. Gan J, Cantwell DP. Dosage effects of methylphenidate on paired associate learning: Positive/negative placebo responders. *Journal of the American Academy of Child Psychiatry*. May 1982;21(3):237-242.
111. Garces K. Atomoxetine for attention deficit/hyperactivity disorder. *Issues in Emerging Health Technologies*. 2003(46):1-4.
112. Garfinkel BD, Brown WA, Klee SH, et al. Neuroendocrine and cognitive responses to amphetamine in adolescents with a history of attention deficit disorder. *Journal of the American Academy of Child Psychiatry*. 1986;25(4):503-508.
113. Garfinkel BD, Webster CD, Sloman L. Individual responses to methylphenidate and caffeine in children with minimal brain dysfunction. *CMAJ: Canadian Medical Association Journal*. 1975;113(8):729-732.
114. Garfinkel BD, Webster CD, Sloman L. Methylphenidate and caffeine in the treatment of children with minimal brain dysfunction. *American Journal of Psychiatry*. 1975;132(7):723-728.
115. Garfinkel BD, Webster CD, Sloman L. Responses to methylphenidate and varied doses of caffeine in children with attention deficit disorder. *Canadian Journal of Psychiatry / Revue Canadienne de Psychiatrie*. 1981;26(6):395-401.
116. Garfinkel BD, Wender PH, Sloman L, O'Neill I. Tricyclic antidepressant and methylphenidate treatment of attention deficit disorder in children. *J Am Acad Child Psychiatr*. 1983;22(4):343-348.
117. Garland M, Kirkpatrick P. Atomoxetine hydrochloride. *Nature Reviews Drug Discovery*. 2004;3(5):385-386.
118. Ghuman JK, Ginsburg GS, Subramaniam G, Ghuman HS, Kau AS, Riddle MA. Psychostimulants in preschool children with attention-deficit/hyperactivity disorder: clinical evidence from a developmental disorders institution. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2001;40(5):516-524.
119. Gillberg C, Melander H, von Knorring AL, et al. Long-term stimulant treatment of children with attention-deficit hyperactivity disorder symptoms. A randomized, double-blind, placebo-controlled trial.[comment]. *Archives of General Psychiatry*. 1997;54(9):857-864.
120. Gittelman-Klein R, Klein DF, Katz S, Saraf K, Pollack E. Comparative effects of

- methylphenidate and thioridazine in hyperkinetic children. I. *Archives of General Psychiatry*. 1976;33(10):1217-1231.
121. Gonzalez. Tolerability of OROS MPH 18mg and 36mg in epilepsy and attention deficit/hyperactivity disorder. Paper presented at: International League Against Epilepsy Annual Congress; Aug 28 - Sept 1, 2005; Paris France.
122. Greenberg LM, Deem MA, McMahon S. Effects of dextroamphetamine, chlorpromazine, and hydroxyzine on behavior and performance in hyperactive children. *American Journal of Psychiatry*. 1972;129(5):532-539.
123. Greenhill LL. Preschool ADHD treatment study (PATs): Science and controversy. *Economics of Neuroscience*. 2001;3(5):49-53.
124. Greenhill LL, Abikoff HB, Arnold LE, et al. Medication treatment strategies in the MTA Study: relevance to clinicians and researchers. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1996;35(10):1304-1313.
125. Greenhill LL, Cooper T, Solomon M, Fried J, Cornblatt B. Methylphenidate salivary levels in children. *Psychopharmacology Bulletin*. 1987;23(1):115-119.
126. Greenhill LL, Swanson JM, Vitiello B, et al. Impairment and deportment responses to different methylphenidate doses in children with ADHD: the MTA titration trial. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2001;40(2):180-187.
127. Gross MD. Imipramine in the treatment of minimal brain dysfunction in children. *Psychosomatics*. 1973;14(5):283-285.
128. Gross-Tsur V. Carbamazepine and methylphenidate. *Journal of the American Academy of Child & Adolescent Psychiatry*. Jun 1999;38(6):637.
129. Gualtieri CT, Hicks RE, Mayo JP, Schroeder SR. The persistence of stimulant effects in chronically treated children: further evidence of an inverse relationship between drug effects and placebo levels of response. *Psychopharmacology*. 1984;83(1):44-47.
130. Gulley V, Northup J. Comprehensive school-based behavioral assessment of the effects of methylphenidate. *Journal of Applied Behavior Analysis*. 1997;30(4):627-638.
131. Gulley V, Northup J, Hupp S, Spera S, LeVelle J, Ridgway A. Sequential evaluation of behavioral treatments and methylphenidate dosage for children with attention deficit hyperactivity disorder. *Journal of Applied Behavior Analysis*. 2003;36(3):375-378.
132. Handen BL, Janosky J, McAuliffe S, Breaux AM, Feldman H. Prediction of response to methylphenidate among children with ADHD and mental retardation. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1994;33(8):1185-1193.
133. Hazell PL, Stuart JE. A randomized controlled trial of clonidine added to psychostimulant medication for hyperactive and aggressive children. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2003;42(8):886-894.
134. Hechtman L. Growth and cardiovascular measures in hyperactive individuals as young adults and in matched normal controls. *Canadian Medical Association Journal*. 1978;118:1247-1250.
135. Hinshaw SP, Buhrmester D, Heller T. Anger control in response to verbal provocation: effects of stimulant medication for boys with ADHD. *Journal of Abnormal Child Psychology*. 1989;17(4):393-407.
136. Hinshaw SP, Heller T, McHale JP. Covert antisocial behavior in boys with attention-deficit hyperactivity disorder: external validation and effects of methylphenidate. *Journal of Consulting & Clinical Psychology*. 1992;60(2):274-281.

137. Hinshaw SP, Heller T, McHale JP. Covert antisocial behavior in boys with attention-deficit hyperactivity disorder: External validation and effects of methylphenidate. *Annual Progress in Child Psychiatry & Child Development*. 1993.
138. Hinshaw SP, Henker B, Whalen CK. Cognitive-behavioral and pharmacologic interventions for hyperactive boys: comparative and combined effects. *Journal of Consulting & Clinical Psychology*. 1984;52(5):739-749.
139. Hinshaw SP, Henker B, Whalen CK, Erhardt D, Dunnington RE, Jr. Aggressive, prosocial, and nonsocial behavior in hyperactive boys: dose effects of methylphenidate in naturalistic settings. *Journal of Consulting & Clinical Psychology*. 1989;57(5):636-643.
140. Hoeppner J-AB, Hale J, Bradley A, et al. A clinical protocol for determining methylphenidate dosage levels in ADHD. *Journal of Attention Disorders*. Apr 1997;2(1):19-30.
141. Ialongo NS, Lopez M, Horn WF, Pascoe JM, et al. Effects of psychostimulant medication on self-perceptions of competence, control, and mood in children with attention deficit hyperactivity disorder. *Journal of Clinical Child Psychology*. Jun 1994;23(2):161-173.
142. Jadad AR, Booker L, Gault M, et al. The treatment of attention-deficit hyperactivity disorder: An annotated bibliography and critical appraisal of published systematic reviews and metaanalyses. *Canadian Journal of Psychiatry*. 1999;44(10):1025-1035.
143. Jasinski DR. Abuse liability assessment of atomoxetine in a drug-abusing population. Paper presented at: American College of Neuropsychopharmacology; Dec 7-11, 2003; San Juan, Puerto Rico.
144. Jensen P. Longer term effects of stimulant treatments for Attention-Deficit/Hyperactivity Disorder. *Journal of Attention Disorders*. 2002;6(Suppl 1):S45-56.
145. Johnston C, Fine S. Methods of evaluating methylphenidate in children with attention deficit hyperactivity disorder: acceptability, satisfaction, and compliance. *Journal of Pediatric Psychology*. 1993;18(6):717-730.
146. Johnston C, Pelham WE, Hoza J, Sturges J. Psychostimulant rebound in attention deficit disordered boys. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1988;27(6):806-810.
147. Jonkman LM, Kemner C, Verbaten MN, et al. Effects of methylphenidate on event-related potentials and performance of attention-deficit hyperactivity disorder children in auditory and visual selective attention tasks. *Biological Psychiatry*. 1997;41(6):690-702.
148. Jonkman LM, Kemner C, Verbaten MN, et al. Perceptual and response interference in children with attention-deficit hyperactivity disorder, and the effects of methylphenidate. *Psychophysiology*. 1999;36(4):419-429.
149. Kavale K. The efficacy of stimulant drug treatment for hyperactivity: a meta-analysis. *Journal of Learning Disabilities*. 1982;15:280-289.
150. Kelly KL, Rapport MD, DuPaul GJ. Attention deficit disorder and methylphenidate: a multi-step analysis of dose-response effects on children's cardiovascular functioning. *International Clinical Psychopharmacology*. 1988;3(2):167-181.
151. Kemner C, Jonkman LM, Kenemans J, Bocker KB, Verbaten MN, van Engeland H. Sources of auditory selective attention and the effects of methylphenidate in children with attention-deficit/hyperactivity disorder. *Biological Psychiatry*. Apr 2004;55(7):776-778.

152. Kent JD, Blader JC, Koplewicz HS, Abikoff H, Foley CA. Effects of late-afternoon methylphenidate administration on behavior and sleep in attention-deficit hyperactivity disorder.[comment]. *Pediatrics*. 1995;96(2 Pt 1):320-325.
153. Kent MA, Camfield CS, Camfield PR. Double-blind methylphenidate trials: practical, useful, and highly endorsed by families. *Archives of Pediatrics & Adolescent Medicine*. 1999;153(12):1292-1296.
154. Klein RG, Abikoff H. Behavior therapy and methylphenidate in the treatment of children with ADHD. *Journal of Attention Disorders*. Jul 1997;2(2):89-114.
155. Klorman R, Brumaghim JT, Fitzpatrick PA, Borgstedt AD, Strauss J. Clinical and cognitive effects of methylphenidate on children with attention deficit disorder as a function of aggression/oppositionality and age. *Journal of Abnormal Psychology*. 1994;103(2):206-221.
156. Klorman R, Brumaghim JT, Salzman LF, et al. Effects of methylphenidate on attention-deficit hyperactivity disorder with and without aggressive/noncompliant features. *Journal of Abnormal Psychology*. 1988;97(4):413-422.
157. Klorman R, Salzman LF, Bauer LO, Coons HW, Borgstedt AD, Halpern WI. Effects of two doses of methylphenidate on cross-situational and borderline hyperactive children's evoked potentials. *Electroencephalography & Clinical Neurophysiology*. 1983;56(2):169-185.
158. Kolko DJ, Bukstein OG, Barron J. Methylphenidate and behavior modification in children with ADHD and comorbid ODD or CD: main and incremental effects across settings. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1999;38(5):578-586.
159. Kollins SH, Shapiro SK, Newland MC, Abramowitz A. Discriminative and participant-rated effects of methylphenidate in children diagnosed with attention deficit hyperactivity disorder (ADHD). *Experimental & Clinical Psychopharmacology*. 1998;6(4):375-389.
160. Konrad K, Gunther T, Hanisch C, Herpertz-Dahlmann B. Differential effects of methylphenidate on attentional functions in children with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2004;43(2):191-198.
161. Kratochvil C, Newcorn J, Arnold L, et al. Atomoxetine alone or combined with fluoxetine for treating ADHD with comorbid depressive or anxiety symptoms. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2005;44(9):915-924.
162. Krusch DA, Klorman R, Brumaghim JT, Fitzpatrick PA, Borgstedt AD, Strauss J. Methylphenidate slows reactions of children with attention deficit disorder during and after an error. *Journal of Abnormal Child Psychology*. 1996;24(5):633-650.
163. Leibson CL, Long KH. Economic Implications of Attention-Deficit Hyperactivity Disorder for Healthcare Systems. *PharmacoEconomics*. 2003;21(17):1239-1262.
164. Levin FR, Evans SM, Kleber HD. Methylphenidate Treatment for Cocaine Abusers with Adult Attention-Deficit/Hyperactivity Disorder. *NIDA Research Monograph*. Vol. 1999;179:39.
165. Levin FR, Evans SM, McDowell DM, Brooks DJ, Nunes E. Bupropion treatment for cocaine abuse and adult attention-deficit/hyperactivity disorder. *Journal of Addictive Diseases*. 2002;21(2):1-16.
166. Levy F, Hobbes G. The action of stimulant medication in attention deficit disorder with

- hyperactivity: dopaminergic, noradrenergic, or both?[comment]. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1988;27(6):802-805.
167. Levy F, Hobbes G. Does haloperidol block methylphenidate? Motivation or attention? *Psychopharmacology*. 1996;126(1):70-74.
168. Lewis JA, Young R. Deanol and methylphenidate in minimal brain dysfunction. *Clinical Pharmacology & Therapeutics*. 1975;17(5):534-540.
169. Lipkin PH, Goldstein IJ, Adelman AR. Tics and dyskinesias associated with stimulant treatment in attention-deficit hyperactivity disorder. *Archives of Pediatrics & Adolescent Medicine*. 1994;148(8):859-861.
170. Losier BJ, McGrath PJ, Klein RM. Error patterns on the continuous performance test in non-medicated and medicated samples of children with and without ADHD: a meta-analytic review. *Journal of Child Psychology & Psychiatry & Allied Disciplines*. 1996;37(8):971-987.
171. Lufi D, Parish-Plass J, Gai E. The effect of methylphenidate on the cognitive and personality functioning of ADHD children. *Israel Journal of Psychiatry & Related Sciences*. 1997;34(3):200-209.
172. Mahalik DM, Carmel PW, Greenberg JP, et al. Psychopharmacologic treatment of acquired attention disorders in children with brain injury. *Pediatric Neurosurgery*. 1998;29(3):121-126.
173. Malone MA, Kershner JR, Siegel L. The effects of methylphenidate on levels of processing and laterality in children with attention deficit disorder. *Journal of Abnormal Child Psychology*. 1988;16(4):379-395.
174. Malone MA, Swanson JM. Effects of methylphenidate on impulsive responding in children with attention-deficit hyperactivity disorder. *Journal of Child Neurology*. 1993;8(2):157-163.
175. Matza LS, Rentz AM, Secnik K, et al. The link between health-related quality of life and clinical symptoms among children with attention-deficit hyperactivity disorder. *Journal of developmental and behavioral pediatrics : JDBP*. 2004;25(3):166-174.
176. Mayes SD, Bixler EO. Reliability of global impressions for assessing methylphenidate effects in children with attention-deficit hyperactivity disorder. *Perceptual & Motor Skills*. 1993;77(3 Pt 2):1215-1218.
177. Mayes SD, Crites DL, Bixler EO, Humphrey FJ, 2nd, Mattison RE. Methylphenidate and ADHD: influence of age, IQ and neurodevelopmental status. *Developmental Medicine & Child Neurology*. 1994;36(12):1099-1107.
178. McBride MC. An individual double-blind crossover trial for assessing methylphenidate response in children with attention deficit disorder.[comment]. *Journal of Pediatrics*. 1988;113(1 Pt 1):137-145.
179. McBurnett. Effectiveness of OROS(R) Methylphenidate in patients with or without comorbid oppositional disorder and conduct disorder. Paper presented at: The American Academy of Child and Adolescent Psychiatry for Presentation Annual Meeting; Oct 18-21, 2005; Toronto, Canada.
180. McCracken JT, Biederman J, Greenhill LL, et al. Analog classroom assessment of a once-daily mixed amphetamine formulation, SLI381 (Adderall XR), in children with ADHD. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2003;42(6):673-683.
181. McKeage K, Scott LJ. SLI-381 (Adderall XR(registered trademark)). *CNS Drugs*.

- 2003;17(9):669-675.
182. Mehta MA, Goodyer IM, Sahakian BJ. Methylphenidate improves working memory and set-shifting in AD/HD: Relationships to baseline memory capacity. *Journal of Child Psychology and Psychiatry and Allied Disciplines*. 2004;45(2):293-305.
 183. Milich R, Carlson CL, Pelham WE, Jr., Licht BG. Effects of methylphenidate on the persistence of ADHD boys following failure experiences. *Journal of Abnormal Child Psychology*. 1991;19(5):519-536.
 184. Milich R, Licht BG, Murphy DA, Pelham WE. Attention-deficit hyperactivity disorder boys' evaluations of and attributions for task performance on medication versus placebo. *Journal of Abnormal Psychology*. Aug 1989;98(3):280-284.
 185. Millichap JG, Millichap M. Growth of hyperactive children. *New England Journal of Medicine*. 1975;292:1300.
 186. Mohammadi MR, Kashani L, Akhondzadeh S, Izadian ES, Ohadinia S. Efficacy of theophylline compared to methylphenidate for the treatment of attention-deficit hyperactivity disorder in children and adolescents: A pilot double-blind randomized trial. *Journal of Clinical Pharmacy and Therapeutics*. 2004;29(2):139-144.
 187. Murray LK, Kollins SH. Effects of methylphenidate on sensitivity to reinforcement in children diagnosed with attention deficit hyperactivity disorder: An application of the matching law. *Journal of Applied Behavior Analysis*. Win 2000;33(4):573-591.
 188. Nemzer ED, Arnold LE, Votolato NA, McConnell H. Amino acid supplementation as therapy for attention deficit disorder. *Journal of the American Academy of Child Psychiatry*. 1986;25(4):509-513.
 189. Noble RE. Anorexigenic activity of intermittent dextroamphetamine with and without meprobamate. *Current Therapeutic Research, Clinical & Experimental*. 1972;14(4):162-167.
 190. Nolan EE, Gadow KD. Children with ADHD and tic disorder and their classmates: behavioral normalization with methylphenidate. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1997;36(5):597-604.
 191. Nolan EE, Gadow KD, Sprafkin J. Stimulant medication withdrawal during long-term therapy in children with comorbid attention-deficit hyperactivity disorder and chronic multiple tic disorder. *Pediatrics*. 1999;103(4 Pt 1):730-737.
 192. Northup J, Fusilier I, Swanson V, Roane H, Borrero J. An evaluation of methylphenidate as a potential establishing operation for some common classroom reinforcers. *Journal of Applied Behavior Analysis*. 1997;30(4):615-625.
 193. Oosterheld JR, Kofoed L, Tervo R, Fogas B, Wilson A, Fiechtner H. Effectiveness of methylphenidate in Native American children with fetal alcohol syndrome and attention deficit/hyperactivity disorder: a controlled pilot study. *Journal of Child & Adolescent Psychopharmacology*. 1998;8(1):39-48.
 194. Orio F, Padovano N, Cinquanta L, et al. Growth rate and growth hormone response to growth hormone-releasing hormone challenge in slowly growing children during chronic administration of clonidine. *Journal of Endocrinological Investigation*. 1995;18(1):63-67.
 195. O'Toole K, Abramowitz A, Morris R, Dulcan M. Effects of methylphenidate on attention and nonverbal learning in children with attention-deficit hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1997;36(4):531-538.
 196. Overtom CC, Verbaten MN, Kemner C, et al. Effects of methylphenidate, desipramine,

- and L-dopa on attention and inhibition in children with Attention Deficit Hyperactivity Disorder. *Behavioural Brain Research*. 2003;145(1-2):7-15.
197. Pataki CS, Carlson GA, Kelly KL, Rapport MD, Biancaniello TM. Side effects of methylphenidate and desipramine alone and in combination in children. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1993;32(5):1065-1072.
198. Pearson DA, Santos CW, Roache JD, et al. Treatment effects of methylphenidate on behavioral adjustment in children with mental retardation and ADHD. *Journal of the American Academy of Child & Adolescent Psychiatry*. Feb 2003;42(2):209-216.
199. Pearson DA, Santos CW, Roache JD, Loveland KA, et al. Effects of methylphenidate on behavioral adjustment in children with mental retardation and ADHD: Preliminary findings from a study in progress. *Journal of Developmental & Physical Disabilities*. Dec 1996;8(4):313-333.
200. Peeke S, Halliday R, Callaway E, Prael R, Reus V. Effects of two doses of methylphenidate on verbal information processing in hyperactive children. *Journal of Clinical Psychopharmacology*. 1984;4(2):82-88.
201. Pelham WE, Bender ME, Caddell J, Booth S, Moorner SH. Methylphenidate and children with attention deficit disorder. Dose effects on classroom academic and social behavior. *Archives of General Psychiatry*. 1985;42(10):948-952.
202. Pelham WE, Jr., Carlson C, Sams SE, Vallano G, Dixon MJ, Hoza B. Separate and combined effects of methylphenidate and behavior modification on boys with attention deficit-hyperactivity disorder in the classroom. *Journal of Consulting & Clinical Psychology*. 1993;61(3):506-515.
203. Pelham WE, Hoffman MT, and Lock T. Evaluation of once-a-day OROS methylphenidate HCl (MPH) extended release tablets vs MPH tid in children with ADHD in a laboratory setting. *Pediatric Research*. 2000;47(4):31A.
204. Pelham WE, Hoza B, Pillow DR, et al. Effects of methylphenidate and expectancy on children with ADHD: behavior, academic performance, and attributions in a summer treatment program and regular classroom settings. *Journal of Consulting & Clinical Psychology*. 2002;70(2):320-335.
205. Pelham WE, Kipp HL, Gnagy EM, Hoza B, Trane ST. Effects of methylphenidate and expectancy on ADHD children's performance, self-evaluations, persistence, and attributions on a cognitive task. *Experimental & Clinical Psychopharmacology*. 1997;5(1):3-13.
206. Pelham WE, Jr., McBurnett K, Harper GW, et al. Methylphenidate and baseball playing in ADHD children: who's on first? *Journal of Consulting & Clinical Psychology*. 1990;58(1):130-133.
207. Pelham WE, Milich R, Cummings EM, Murphy DA, Schaughency EA, Greiner AR. Effects of background anger, provocation, and methylphenidate on emotional arousal and aggressive responding in attention-deficit hyperactivity disorder boys with and without concurrent aggressiveness. *Journal of Abnormal Child Psychology*. 1991;19(4):407-426.
208. Pelham WE, Milich R, Walker JL. Effects of continuous and partial reinforcement and methylphenidate on learning in children with Attention Deficit Disorder. *Journal of Abnormal Psychology*. 1986;95(4):319-325.
209. Pelham WE, Murphy DA, Vannatta K, et al. Methylphenidate and attributions in boys with attention-deficit hyperactivity disorder. *Journal of Consulting & Clinical*

- Psychology*. 1992;60(2):282-292.
210. Pelham WE, Jr., Waschbusch DA, Hoza B, Pillow DR, Gnagy EM. Effects of methylphenidate and expectancy on performance, self-evaluations, persistence, and attributions on a social task in boys with ADHD. *Experimental & Clinical Psychopharmacology*. 2001;9(4):425-437.
211. Perwien AR, Faries DE, Kratochvil CJ, Sumner CR, Kelsey DK, Allen AJ. Improvement in health-related quality of life in children with ADHD: an analysis of placebo controlled studies of atomoxetine.[see comment]. *Journal of Developmental & Behavioral Pediatrics*. 2004;25(4):264-271.
212. Pliszka SR. Effect of anxiety on cognition, behavior, and stimulant response in ADHD. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1989;28(6):882-887.
213. Pliszka SR. Effect of anxiety on cognition, behavior, and stimulant response in ADHD. *Annual Progress in Child Psychiatry & Child Development*. 1990;454(466):454.
214. Pliszka SR. The use of psychostimulants in the pediatric patient. *Pediatric Clinics of North America*. 1998;45(5):1085-1098.
215. Popper CW. Combining methylphenidate and clonidine: Pharmacologic questions and news reports about sudden death. *Journal of Child & Adolescent Psychopharmacology*. Fall 1995;5(3):157-166.
216. Porrino LJ, Rapoport JL, Behar D, Ismond DR, Bunney WE, Jr. A naturalistic assessment of the motor activity of hyperactive boys. II. Stimulant drug effects. *Archives of General Psychiatry*. 1983;40(6):688-693.
217. Potashkin BD, Beckles N. Relative efficacy of ritalin and biofeedback treatments in the management of hyperactivity. *Biofeedback & Self Regulation*. 1990;15(4):305-315.
218. Poulton A, Cowell CT. Slowing of growth in height and weight on stimulants: a characteristic pattern. *Journal of Paediatrics & Child Health*. 2003;39(3):180-185.
219. Ramchandani P, Joughin C, Zwi M. Attention deficit hyperactivity disorder in children.[update in Clin Evid. 2002 Dec;(8):280-90; PMID: 12603883]. *Clinical Evidence*. 2002(7):262-271.
220. Rapoport JL, Quinn PO, Bradbard G, Riddle KD, Brooks E. Imipramine and methylphenidate treatments of hyperactive boys. *Archives of General Psychiatry*. 1974;30(6):789-793.
221. Rapport MD, Denney C. Titrating methylphenidate in children with attention-deficit/hyperactivity disorder: is body mass predictive of clinical response? *Journal of the American Academy of Child & Adolescent Psychiatry*. 1997;36(4):523-530.
222. Rapport MD, Denney C, DuPaul GJ, Gardner MJ. Attention deficit disorder and methylphenidate: normalization rates, clinical effectiveness, and response prediction in 76 children. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1994;33(6):882-893.
223. Rapport MD, DuPaul GJ, Smith NF. Rate-dependency and hyperactivity: methylphenidate effects on operant responding. *Pharmacology, Biochemistry & Behavior*. 1985;23(1):77-83.
224. Rapport MD, DuPaul GJ, Stoner G, Birmingham BK, Masse G. Attention deficit disorder with hyperactivity: differential effects of methylphenidate on impulsivity. *Pediatrics*. 1985;76(6):938-943.
225. Rapport MD, DuPaul GJ, Stoner G, Jones TJ. Comparing classroom and clinic measures

- of attention deficit disorder: differential, idiosyncratic, and dose-response effects of methylphenidate. *Journal of Consulting & Clinical Psychology*. 1986;54(3):334-341.
226. Rapport MD, Jones J, DuPaul GJ, Kelly KL, et al. Attention deficit disorder and methylphenidate: Group and single-subject analyses of dose effects on attention in clinic and classroom settings. *Journal of Clinical Child Psychology*. Dec 1987;16(4):329-338.
 227. Rapport MD, Loo S, Denney C. The paired associate learning task: Is it an externally valid instrument for assessing methylphenidate response in children with attention deficit disorder? *Journal of Psychopathology & Behavioral Assessment*. 1995;17(2):125-144.
 228. Rapport MD, Loo S, Isaacs P, Goya S, Denney C, Scanlan S. Methylphenidate and attentional training. Comparative effects on behavior and neurocognitive performance in twin girls with attention-deficit/hyperactivity disorder. *Behavior Modification*. 1996;20(4):428-430.
 229. Rapport MD, Quinn SO, DuPaul GJ, Quinn EP, Kelly KL. Attention deficit disorder with hyperactivity and methylphenidate: the effects of dose and mastery level on children's learning performance. *Journal of Abnormal Child Psychology*. 1989;17(6):669-689.
 230. Rapport MD, Randall R, Moffitt C. Attention-Deficit/Hyperactivity Disorder and methylphenidate: a dose-response analysis and parent-child comparison of somatic complaints. *Journal of Attention Disorders*. 2002;6(1):15-24.
 231. Rapport MD, Stoner G, DuPaul GJ, Birmingham BK, Tucker S. Methylphenidate in hyperactive children: differential effects of dose on academic, learning, and social behavior. *Journal of Abnormal Child Psychology*. 1985;13(2):227-243.
 232. Rapport MD, Stoner G, DuPaul GJ, Kelly KL, Tucker SB, Schoeler T. Attention deficit disorder and methylphenidate: a multilevel analysis of dose-response effects on children's impulsivity across settings. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1988;27(1):60-69.
 233. Reid MK, Borkowski JG. Effects of methylphenidate (Ritalin) on information processing in hyperactive children. *Journal of Abnormal Child Psychology*. 1984;12(1):169-185.
 234. Richardson E, Kupietz SS, Winsberg BG, Maitinski S, Mendell N. Effects of methylphenidate dosage in hyperactive reading-disabled children: II. Reading achievement. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1988;27(1):78-87.
 235. Riddle KD, Rapoport JL. A 2-year follow-up of 72 hyperactive boys. Classroom behavior and peer acceptance. *Journal of Nervous & Mental Disease*. 1976;162(2):126-134.
 236. Rubia K, Noorloos J, Smith A, Gunning B, Sergeant J. Motor Timing Deficits in Community and Clinical Boys with Hyperactive Behavior: The Effect of Methylphenidate on Motor Timing. *Journal of Abnormal Child Psychology*. Feb 2003;31(3):301-313.
 237. Schachar RJ, Tannock R, Cunningham C, Corkum PV. Behavioral, situational, and temporal effects of treatment of ADHD with methylphenidate. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1997;36(6):754-763.
 238. Schain RJ, Reynard CL. Observations on effects of a central stimulant drug (methylphenidate) in children with hyperactive behavior. *Pediatrics*. 1975;55(5):709-716.
 239. Scheres A, Oosterlaan J, Swanson J, et al. The effect of methylphenidate on three forms

- of response inhibition in boys with AD/HD. *Journal of Abnormal Child Psychology*. 2003;31(1):105-120.
240. Schmidt MH, Mocks P, Lay B, et al. Does oligoantigenic diet influence hyperactive/conduct-disordered children--a controlled trial. *European Child & Adolescent Psychiatry*. 1997;6(2):88-95.
 241. Schnipper. Evaluation of participant use and efficacy of an OROS formulation of methylphenidate HCl in individuals with ADHD in a community setting. Paper presented at: Pediatric Societies Meeting; Apr 28-May 1, 2001; Baltimore, Maryland.
 242. Schwan V, Gulka-Tiechko D, Saklofske D. Effects of ritalin on the processing of nonverbal cues in children with ADHD. *Issues in Special Education & Rehabilitation*. 1994;9(2):49-56.
 243. Schwan V, Saklofske D, Yackulic R, Quinn D. WISC-III performance of ADHD children. In: Bracken BA, McCallum RS, eds. *Wechsler Intelligence Scale for Children: Third edition Journal of Psychoeducational Assessment Advances in psychoeducational assessment* Saskatoon, SK, Canada: University of Saskatchewan, Dept. for the Education of Exceptional Children; 1993:56-70.
 244. Sebrechts MM, Shaywitz SE, Shaywitz BA, Jatlow P, Anderson GM, Cohen DJ. Components of attention, methylphenidate dosage, and blood levels in children with attention deficit disorder. *Pediatrics*. 1986;77(2):222-228.
 245. Shea VT. State-dependent learning in children receiving methylphenidate. *Psychopharmacology*. 1982;78(3):266-270.
 246. Shekim WO, Bylund DB, Alexson J, et al. Platelet MAO and measures of attention and impulsivity in boys with attention deficit disorder and hyperactivity. *Psychiatry Research*. 1986;18(2):179-188.
 247. Shevell M, Schreiber R. Pemoline-associated hepatic failure: A critical analysis of the literature. *Pediatric Neurology*. 1997;16(1):14-16.
 248. Short EJ, Manos MJ, Findling RL, Schubel EA. A prospective study of stimulant response in preschool children: insights from ROC analyses. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2004;43(3):251-259.
 249. Simeon JG, Ferguson H, Van Wyck Fleet J. Bupropion effects in attention deficit and conduct disorders. *Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie*. Aug 1986;31(6):581-585.
 250. Smith BH, Pelham WE, Jr., Gnagy E, Molina B, Evans S. The reliability, validity, and unique contributions of self-report by adolescents receiving treatment for attention-deficit/hyperactivity disorder. *Journal of Consulting & Clinical Psychology*. 2000;68(3):489-499.
 251. Smith BH, Pelham WE, Gnagy E, Yudell RS. Equivalent effects of stimulant treatment for attention-deficit hyperactivity disorder during childhood and adolescence. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1998;37(3):314-321.
 252. Snyder R, Turgay A, Aman M, et al. Effects of risperidone on conduct and disruptive behavior disorders in children with subaverage IQs. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2002;41(9):1026-1036.
 253. Solanto MV. Behavioral effects of low-dose methylphenidate in childhood Attention Deficit Disorder: Implications for a mechanism of stimulant drug action. *Journal of the American Academy of Child Psychiatry*. 1986;25(1):96-101.
 254. Solanto MV, Wender EH. Does methylphenidate constrict cognitive functioning? *Journal*

- of the American Academy of Child & Adolescent Psychiatry. 1989;28(6):897-902.
255. Solanto MV, Wender EH. "Does methylphenidate constrict cognitive functioning?": Erratum. *Journal of the American Academy of Child & Adolescent Psychiatry*. Jan 1990;29(1):156.
 256. Solanto MV, Wender EH, Bartell SS. Effects of methylphenidate and behavioral contingencies on sustained attention in attention-deficit hyperactivity disorder: a test of the reward dysfunction hypothesis. *Journal of Child & Adolescent Psychopharmacology*. 1997;7(2):123-136.
 257. Spencer T, Biederman J, Ciccone P, et al. PET study examining pharmacokinetics, detection and likeability, and dopamine transporter receptor occupancy of short- and long-acting oral methylphenidate. *American Journal of Psychiatry*. Mar 2006;163(3):387-395.
 258. Spencer TJ, Biederman J, Harding M, O'Donnell D, Faraone SV, Wilens TE. Growth deficits in ADHD children revisited: evidence for disorder-associated growth delays? *Journal of the American Academy of Child & Adolescent Psychiatry*. 1996;35(11):1460-1469.
 259. Spiga R, Pearson DA, Broitman M, Santos CW. Effects of methylphenidate on cooperative responding in children with attention deficit-hyperactivity disorder. *Experimental & Clinical Psychopharmacology*. Nov 1996;4(4):451-458.
 260. Sprafkin J, Gadow KD. Double-blind versus open evaluations of stimulant drug response in children with attention-deficit hyperactivity disorder. *Journal of Child & Adolescent Psychopharmacology*. 1996;6(4):215-228.
 261. Stein MA, Blondis TA, Schnitzler ER, et al. Methylphenidate dosing: twice daily versus three times daily. *Pediatrics*. 1996;98(4 Pt 1):748-756.
 262. Stein MA, Sarampote CS, Waldman ID, et al. A dose-response study of OROS methylphenidate in children with attention-deficit/hyperactivity disorder. *Pediatrics*. 2003;112(5):e404.
 263. Sverd J, Gadow KD, Paolicelli LM. Methylphenidate treatment of attention-deficit hyperactivity disorder in boys with Tourette's syndrome. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1989;28(4):574-579.
 264. Swanson J, Greenhill L, Pelham W, Wilens T, Wolraich M, et al. Initiating Concerta (OROS methylphenidate HCl) qd in children with attention-deficit hyperactivity disorder. *Journal of Clinical Research*. 2000;3:59-76.
 265. Swanson J, Wigal S, Greenhill L, et al. Objective and subjective measures of the pharmacodynamic effects of Adderall in the treatment of children with ADHD in a controlled laboratory classroom setting. *Psychopharmacology Bulletin*. 1998;34(1):55-60.
 266. Swanson JM, Gupta S, Williams L, Agler D, Lerner M, Wigal S. Efficacy of a new pattern of delivery of methylphenidate for the treatment of ADHD: effects on activity level in the classroom and on the playground. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2002;41(11):1306-1314.
 267. Swanson JM, Sandman CA, Deutsch C, Baren M. Methylphenidate hydrochloride given with or before breakfast: I. Behavioral, cognitive, and electrophysiologic effects. *Pediatrics*. 1983;72(1):49-55.
 268. Swanson JM, Wigal S, Greenhill LL, et al. Analog classroom assessment of Adderall (R) in children with ADHD. *Journal of the American Academy of Child & Adolescent*

- Psychiatry*. 1998a;37(5):519-526.
269. Swanson JM, Wigal SB, and Lemer MA. Comparison of the efficacy and safety of OROS methylphenidate HCl with methylphenidate tid and placebo in children with ADHD. *Pediatric Research*. 2000;47(4 suppl):34A.
 270. Swanson JM, Wigal SB, Udre D, et al. Evaluation of individual subjects in the analog classroom setting: I. Examples of graphical and statistical procedures for within-subject ranking of responses to different delivery patterns of methylphenidate. *Psychopharmacology Bulletin*. 1998b;34(4):825-832.
 271. Swanson JM, Wigal SB, Wigal T, et al. A comparison of once-daily extended-release methylphenidate formulations in children with attention-deficit/hyperactivity disorder in the laboratory school (the Comacs Study). *Pediatrics*. 2004;113(3 Pt 1):e206-216.
 272. Tannock R, Fine J, Heintz T, Schachar RJ. A linguistic approach detects stimulant effects in two children with attention-deficit hyperactivity disorder. *Journal of Child & Adolescent Psychopharmacology*. 1995;5(3):177-189.
 273. Tannock R, Ickowicz A, Schachar R. Differential effects of methylphenidate on working memory in ADHD children with and without comorbid anxiety. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1995;34(7):886-896.
 274. Tannock R, Martinussen R, Frijters J. Naming speed performance and stimulant effects indicate effortful, semantic processing deficits in attention-deficit/hyperactivity disorder. *Journal of Abnormal Child Psychology*. 2000;28(3):237-252.
 275. Tannock R, Schachar R. Methylphenidate and cognitive perseveration in hyperactive children. *Journal of Child Psychology & Psychiatry & Allied Disciplines*. 1992;33(7):1217-1228.
 276. Tannock R, Schachar R, Logan G. Methylphenidate and cognitive flexibility: dissociated dose effects in hyperactive children. *Journal of Abnormal Child Psychology*. 1995;23(2):235-266.
 277. Tannock R, Schachar R, Logan GD. Does methylphenidate induce overfocusing in hyperactive children? *Journal of Clinical Child Psychology*. 1993;22(1):28-41.
 278. Tannock R, Schachar RJ, Carr RP, Chajczyk D, Logan GD. Effects of methylphenidate on inhibitory control in hyperactive children. *Journal of Abnormal Child Psychology*. 1989;17(5):473-491.
 279. Tannock R, Schachar RJ, Carr RP, Logan GD. Dose-response effects of methylphenidate on academic performance and overt behavior in hyperactive children. *Pediatrics*. 1989;84(4):648-657.
 280. Taylor E, Schachar R, Thorley G, Wieselberg HM, Everitt B, Rutter M. Which boys respond to stimulant medication? A controlled trial of methylphenidate in boys with disruptive behaviour. *Psychological Medicine*. 1987;17(1):121-143.
 281. Teicher MH, Polcari A, Anderson CM, Andersen SL, Lowen SB, Navalta CP. Rate dependency revisited: understanding the effects of methylphenidate in children with attention deficit hyperactivity disorder. *Journal of Child & Adolescent Psychopharmacology*. 2003;13(1):41-51.
 282. Tepner R, Michelson D, Wernicke J, et al. Placebo controlled trials of atomoxetine for adhd in children, adolescents, and adults. *International Journal of Neuropsychopharmacology*. 2002;5(Suppl 1):S162-163.
 283. Tervo RC, Azuma S, Fogas B, Fiechtner H. Children with ADHD and motor dysfunction compared with children with ADHD only.[erratum appears in Dev Med Child Neurol

- 2002 Sep;44(9):622 Note: Correction of dosage error in abstract.]. *Developmental Medicine & Child Neurology*. 2002;44(6):383-390.
284. Tillery KL, Katz J, Keller WD. Effects of methylphenidate (Ritalin) on auditory performance in children with attention and auditory processing disorders. *Journal of Speech, Language, & Hearing Research*. 2000;43(4):893-901.
 285. Tirosch E, Elhasid R, Kamah SC, Cohen A. Predictive value of placebo methylphenidate. *Pediatric Neurology*. 1993;9(2):131-133.
 286. Tirosch E, Sadeh A, Munvez R, Lavie P. Effects of methylphenidate on sleep in children with attention-deficient hyperactivity disorder. An activity monitor study. *American Journal of Diseases of Children*. 1993;147(12):1313-1315.
 287. Trommer BL, Hoeppner JA, Zecker SG. The go-no go test in attention deficit disorder is sensitive to methylphenidate. *Journal of Child Neurology*. 1991;6(31):S128-131.
 288. Ullmann RK, Sleator EK. Responders, nonresponders, and placebo responders among children with attention deficit disorder. Importance of a blinded placebo evaluation. *Clinical Pediatrics*. 1986;25(12):594-599.
 289. Urman R, Ickowicz A, Fulford P, Tannock R. An exaggerated cardiovascular response to methylphenidate in ADHD children with anxiety. *Journal of Child & Adolescent Psychopharmacology*. 1995;5(1):29-37.
 290. van der Meere J, Shalev R, Borger N, Gross-Tsur V. Sustained attention, activation and MPH in ADHD: a research note. *Journal of Child Psychology & Psychiatry & Allied Disciplines*. 1995;36(4):697-703.
 291. Varley CK, Trupin EW. Double-blind assessment of stimulant medication for attention deficit disorder: a model for clinical application. *American Journal of Orthopsychiatry*. 1983;53(3):542-547.
 292. Vitiello B, Severe JB, Greenhill LL, et al. Methylphenidate dosage for children with ADHD over time under controlled conditions: lessons from the MTA. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2001;40(2):188-196.
 293. Volkow ND, Insel TR. What are the long-term effects of methylphenidate treatment? *Biological Psychiatry*. 2003;54(12):1307-1309.
 294. Von Knorring A-L. Central stimulant treatment in attention deficit-hyperactivity disorder. Long-term effects. *Nordic Journal of Psychiatry*. 1998;52(2):102-103.
 295. Vyse SA, Rapport MD. The effects of methylphenidate on learning in children with ADDH: the stimulus equivalence paradigm. *Journal of Consulting & Clinical Psychology*. 1989;57(3):425-435.
 296. Walker MK, Sprague RL, Sleator EK, Ullmann RK. Effects of methylphenidate hydrochloride on the subjective reporting of mood in children with attention deficit disorder. *Issues in Mental Health Nursing*. 1988;9(4):373-385.
 297. Wallace AE, Kofoed LL. Statistical analysis of single case studies in the clinical setting: The example of methylphenidate trials in children with attention-deficit hyperactivity disorder. *Journal of Child & Adolescent Psychopharmacology*. Fall 1994;4(3):141-150.
 298. Wallander JL, Schroeder SR, Michelli JA, Gualtieri CT. Classroom social interactions of attention deficit disorder with hyperactivity children as a function of stimulant medication. *Journal of Pediatric Psychology*. 1987;12(1):61-76.
 299. Weiss G, Hechtman L, Milroy T, Perlman T. Psychiatric Status of Hyperactives as Adults: A Controlled Prospective 15-Year Follow-Up of 63 Hyperactive Children. *Journal of the American Academy of Child Psychiatry*. 1985;24(2):211-220.

300. Weiss G, Werry J, Minde K, Douglas V, Sykes D. Studies on the hyperactive child. V. *Journal of Child Psychology & Psychiatry & Allied Disciplines*. 1968;9(3):145-156.
301. Wender PH, Reimherr FW. Bupropion treatment of attention-deficit hyperactivity disorder in adults. *American Journal of Psychiatry*. 1990;147(8):1018-1020.
302. Werry JS, Aman MG. Methylphenidate and haloperidol in children. *Archives of General Psychiatry*. 1975;32(6):790-795.
303. Werry JS, Sprague RL. Methylphenidate in children--effect of dosage. *Australian & New Zealand Journal of Psychiatry*. 1974;8(1):9-19.
304. Whalen CK, Henker B, Buhrmester D, Hinshaw SP, Huber A, Laski K. Does stimulant medication improve the peer status of hyperactive children? *Journal of Consulting & Clinical Psychology*. 1989;57(4):545-549.
305. Whalen CK, Henker B, Finck D. Medication effects in the classroom: three naturalistic indicators. *Journal of Abnormal Child Psychology*. 1981;9(4):419-433.
306. Whalen CK, Henker B, Granger DA. Ratings of medication effects in hyperactive children: Viable or vulnerable? *Behavioral Assessment*. 1989;11(2):179-199.
307. Whalen CK, Henker B, Granger DA. Social judgment processes in hyperactive boys: effects of methylphenidate and comparisons with normal peers. *Journal of Abnormal Child Psychology*. 1990;18(3):297-316.
308. Wilens TE, Biederman J, Spencer TJ. Pharmacotherapy of attention deficit hyperactivity disorder in adults. *CNS Drugs*. 1998;9(5):347-356.
309. Wilens TE, Spencer TJ, Biederman J. A review of the pharmacotherapy of adults with attention-deficit/hyperactivity disorder. *Journal of Attention Disorders*. 2002;5(4):189-202.
310. Wilkison PC, Kircher JC, McMahon WM, Sloane HN. Effects of methylphenidate on reward strength in boys with attention-deficit hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1995;34(7):897-901.
311. Williams JI, Cram DM, Tausig FT, Webster E. Relative effects of drugs and diet on hyperactive behaviors: an experimental study. *Pediatrics*. 1978;61(6):811-817.
312. Williams L. Methylphenidate HCl extended-release tablets for children with ADHD: parent treatment preference and satisfaction. *Pediatric Research*. 2001;49(4):429A.
313. Winsberg BG, Kupietz SS, Sverg J, Hungund BL, Young NL. Methylphenidate oral dose plasma concentrations and behavioral response in children. *Psychopharmacology*. 1982;76(4):329-332.
314. Winsberg BG, Press M, Bialer I, Kupietz S. Dextroamphetamine and methylphenidate in the treatment of hyperactive-aggressive children. *Pediatrics*. 1974;53(2):236-241.
315. Wodrich DL, Kush JC. The effect of methylphenidate on teachers' behavioral ratings in specific school situations. *Psychology in the Schools*. Jan 1998;35(1):81-88.
316. Wolraich. Once daily Concerta(R) in the treatment of girls with ADHD. Paper presented at: Children and Adults with Attention Deficit/Hyperactivity Disorder Annual Meeting; Oct 28-30, 2004; Nashville, Tennessee.
317. Wolraich ML. Efficacy and safety of OROS(r) methylphenidate HCl (mph) extended-release tablets (CONCERTA(tm)), conventional MPH, and placebo in children with ADHD. *International Journal of Neuropsychopharmacology*. 2000;3(Supplement 1):S329.
318. Wolraich ML, The Concerta Study G. Evaluation of efficacy and safety of OROS methylphenidate HCl (MPH) extended-release tablets, methylphenidate tid, and

- placebo in children with ADHD. *Pediatric Research*. 2000;47(4):36A.
319. Yellin AM, Hopwood JH, Greenberg LM. Adults and adolescents with attention deficit disorder: clinical and behavioral responses to psychostimulants. *Journal of Clinical Psychopharmacology*. 1982;2(2):133-136.
320. Zeiner P, Bryhn G, Bjercke C, Truyen K, Strand G. Response to methylphenidate in boys with attention-deficit hyperactivity disorder. *Acta Paediatrica*. 1999;88(3):298-303.
321. Zike K. Drugs in maladaptive school behavior. In: Conners CK, ed. *Clinical use of stimulant drugs in children*. Amsterdam: Excerpta Medica; 1974:313.

Appendix F. Previous systematic reviews

Previous systematic reviews of this evidence are numerous.¹⁻²⁰ We included only four systematic reviews that we rated good quality^{14, 16, 20, 21}. The table below summarizes the characteristics and main findings of these four reviews. We rated the other reviews fair-poor quality primarily because they did not use standard methods of study appraisal. Also, many were not comprehensive in searching multiple databases and were nonspecific with regard to eligibility criteria and literature search strategies.

Inclusion criteria (study design, publication date, population characteristics, and interventions) and methods of analysis varied across the good-quality reviews. Despite this, main findings were generally consistent in suggesting that there are no clear differences in short-term efficacy and tolerability between MPH, DEX and pemoline. Additionally, the Jadad review (1999) summarized findings from longer-term, placebo-controlled trials of DEX and MPH that suggest these stimulants are associated with general improvement that persists over time.²⁰ The Jadad review also summarized findings from placebo-controlled trials of MPH, antidepressants, pemoline, nicotine and phenylalanine in adults which suggested that the short-term efficacy of these treatments remained in question at that time.

Our review encompasses studies from all three good-quality reviews, as well as any published since 2001 and those that met our broader scope of interventions.

Summary of good quality systematic reviews

Review	Characteristics	Main findings
King 2004 (Centre for Reviews and Dissemination, Centre for Health Economics, University of York)	Study design: RCTs for efficacy/adverse events; systematic reviews for adverse events Publication date: MPH=1999 and onward; DEX=1997 and onward; atomoxetine=1981 and onward Population: Children and adolescents (≤ 18 years of age) diagnosed with ADHD (including hyperkinetic disorder) Interventions: MPH, DEX, atomoxetine Total # of included studies: 65	In general, inadequate reporting of study methodology limited reliability of results. There was little evidence of consistent differences in short-term efficacy between MPH IR and ER, MPH IR and DEX IR, or MPH IR and atomoxetine. Adequate data regarding potential short-term adverse effects of MPH IR, MPH ER, DEX IR and atomoxetine is lacking.
Schachter 2001 (EPC at University of Ottawa)	Study design: Placebo-controlled RCTs Publication date: 1981 or later Population: ADD with or without hyperactivity; median age=8.7 years Intervention: short-acting MPH Total # of included trials: 62 (2897 patients)	Short-acting MPH demonstrated consistent short-term efficacy in reducing most ADD-related symptoms. Significant short-term harms reported by parents/patients included decreased appetite, insomnia, stomach ache, drowsiness and dizziness.
Jadad 1999 (EPC at McMaster University)	Study design: RCTs Publication date: 1966 or later Population: ADHD in humans Interventions: DEX, MPH, pemoline, clonidine, bupropion, TCAs and SSRIs	<i>Drug vs drug:</i> There were few, if any differences in short-term efficacy between MPH, DEX and pemoline. Results of MPH and TCAs comparisons were conflicting. Body of drug vs drug evidence did not include any studies of clonidine, bupropion or SSRIs. <i>Longer-term therapy</i> (mean duration=20 weeks): Placebo-

Review	Characteristics	Main findings
	Total # of included trials (total # patients not reported): Drug vs drug=22 Long-term therapy=14 Treatment of ADHD in adults=12	controlled trials of DEX or MPH in primarily school-age children suggest trends in general improvement over time regardless of treatment <i>ADHD in adults</i> : Short-term efficacy of MPH inconsistent across placebo-controlled trials <i>Adverse effects</i> : Short-term trials of stimulants most frequently examined sleep disorders/disturbances, headaches, motor tics, decreased appetite/anorexia, abdominal pain and irritability and no differences were reported. Nausea, fatigue and tiredness were also commonly examined and rates were similar for stimulants and antidepressants. Long-term safety data is inadequate to make any conclusions.
Klassen 1998 Klassen 1999 (CCOHTA)	Study design: RCTs Publication date: 1981 or later Population: Children 0-18 years with diagnosis of ADD, ADDH or ADHD Intervention: DEX, MPH or pemoline for ≥ 1 week in duration Total # of included trials: 26 (999 patients)	No clear differences in short-term efficacy were found between MPH, DEX and pemoline. Safety: not reported

References for Appendix E

1. Biederman J, Faraone SV, Monuteaux MC, Grossbard JR. How informative are parent reports of attention-deficit/hyperactivity disorder symptoms for assessing outcome in clinical trials of long-acting treatments? A pooled analysis of parents' and teachers' reports. *Pediatrics*. 2004;113(6 I):1667-1671.
2. Connor DF. Preschool attention deficit hyperactivity disorder: a review of prevalence, diagnosis, neurobiology, and stimulant treatment. *Journal of Developmental & Behavioral Pediatrics*. 2002;23(1 Suppl):S1-9.
3. Connor DF, Glatt SJ, Lopez ID, Jackson D, Melloni Jr. RH. Psychopharmacology and Aggression. I: A Meta-Analysis of Stimulant Effects on Overt/Covert Aggression-Related Behaviors in ADHD. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2002;41(3):253-261.
4. Faraone SV, Biederman J. Efficacy of Adderall for Attention-Deficit/Hyperactivity Disorder: a meta-analysis. *Journal of Attention Disorders*. 2002;6(2):69-75.
5. Faraone SV, Biederman J, Roe C. Comparative efficacy of Adderall and methylphenidate in attention-deficit/hyperactivity disorder: a meta-analysis. *Journal of Clinical Psychopharmacology*. 2002;22(5):468-473.
6. Faraone SV, Wilens T. Does stimulant treatment lead to substance use disorders? *Journal of Clinical Psychiatry*. 2003;64(SUPPL. 11):9-13.
7. Faraone SV, Spencer T, Aleardi M, Pagano C, Biederman J. Meta-Analysis of the Efficacy of Methylphenidate for Treating Adult Attention-Deficit/Hyperactivity Disorder. *Journal of Clinical Psychopharmacology*. 2004;24(1):24-29.
8. Findling RL. Use of quetiapine in children and adolescents. *Journal of Clinical Psychiatry*. 2002;63(Suppl13):27-31.

9. Findling RL, Kusumakar V, Daneman D, Moshang T, De Smedt G, Binder C. Prolactin Levels during Long-Term Risperidone Treatment in Children and Adolescents. *Journal of Clinical Psychiatry*. 2003;64(11):1362-1369.
10. Gerardin P, Cohen D, Mazet P, Flament MF. Drug treatment of conduct disorder in young people. *European Neuropsychopharmacology*. 2002;12(5):361-370.
11. Gilmore A, Milne R. Methylphenidate in children with hyperactivity: review and cost-utility analysis. *Pharmacoepidemiology & Drug Safety*. 2001;10(2):85-94.
12. Greenhill LL, Halperin JM, Abikoff H. Stimulant medications. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1999;38(5):503-512.
13. Jin C, Schachar R. Methylphenidate treatment of attention-deficit/hyperactivity disorder secondary to traumatic brain injury: a critical appraisal of treatment studies. *Cns Spectrums*. 2004;9(3):217-226.
14. Klassen A, Miller A, Raina P, Lee SK, Olsen L. Attention-deficit hyperactivity disorder in children and youth: A quantitative systematic review of the efficacy of different management strategies. *Canadian Journal of Psychiatry*. 1999;44(10):1007-1016.
15. Schachar R, Tannock R. Childhood hyperactivity and psychostimulants: A review of extended treatment studies. *Journal of Child & Adolescent Psychopharmacology*. Sum 1993;3(2):81-97.
16. Schachter HM, Pham B, King J, Langford S, Moher D. How efficacious and safe is short-acting methylphenidate for the treatment of attention-deficit disorder in children and adolescents? A meta-analysis. *CMAJ Canadian Medical Association Journal*. 2001;165(11):1475-1488.
17. Wilens TE, Biederman J, Spencer TJ, Prince J. Pharmacotherapy of adult attention deficit/hyperactivity disorder: a review. *Journal of Clinical Psychopharmacology*. 1995;15(4):270-279.
18. Wilens TE, Faraone SV, Biederman J, Gunawardene S. Does stimulant therapy of attention-deficit/hyperactivity disorder beget later substance abuse? A meta-analytic review of the literature. *Pediatrics*. 2003;111(1):179-185.
19. Connor DF, Fletcher KE, Swanson JM. A meta-analysis of clonidine for symptoms of attention-deficit hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1999;38(12):1551-1559.
20. Jadad AR, Boyle M, Cunningham C, Kim M, Schachar R. Treatment of attention-deficit/hyperactivity disorder. *Evidence Report: Technology Assessment (Summary)*. 1999(11):i-viii, 1-341.
21. King S, Griffin S, Hodges Z, et al. Methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder in children.
http://www.nice.org.uk/pdf/ADHD_assessment_report.pdf